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# CRANIAL ARTERITIS: A CRITICAL EVALUATION OF THE SYNDROME OF "TEMPORAL ARTERITIS" WITH REPORT OF A CASE *

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"TEMPORAL arteritis" is a rare, febrile, self-limited disease of variable duration and unknown etiology. It afflicts the aged of both sexes and is characterized by painful inflammation of the temporal arteries and the general systemic signs and symptoms of malaise, weight loss, anorexia, fever, sweating, and weakness. Since 1932, when Horton, Magath, and Brown first described this symptom complex as an entity, 20 case reports have appeared in the literature. The identity of this disease has been challenged by several authors, notably by Jennings, who states that temporal arteritis cannot be differentiated from periarteritis nodosa. Indeed, in the New York Hospital, temporal arteritis has been noted in a proved case of periarteritis nodosa.

It is the purpose of this paper to attempt an evaluation of "temporal arteritis" as a clinical and pathological entity, with special reference to its differentiation from other forms of arteritis. The following description of temporal arteritis, based on a study of the 20 published case reports and a detailed investigation of our own case, has led us to a broader conception of the nature of this malady.

*Incidence.* The rarity of this disorder is indicated by the paucity of case reports (20) in the 13 years since its first description.

The age incidence is 55 to 80; the incidence is greater in women, being about 3 : 1, and the disease has been noted only in those of the white race residing in the United States of America and England. No seasonal predilection has been observed.

*Symptomatology.* The symptomatology of this disease may be divided into the non-specific complaints of generalized, systemic nature, and those

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complaints directly attributable to inflammation and distention of the temporal and other arteries.

*Non-Specific Complaints.* In every case there have been signs and symptoms which cannot be plausibly related to sterile inflammation of the temporal arteries alone, and which are more suggestive of chronic or subacute infection.

Prevalent symptoms and signs are: weight loss, anorexia, general malaise, fever, sweating, and weakness. The weight loss may be profound (30 pounds), and the patient emaciated.[8] This is probably secondary to anorexia, which, although in certain cases a concomitant of the excruciating pain and headache, may antedate the onset of pain, as in our case. Sweating is a common symptom, and in our patient occurred during the stage of acute arterial inflammation.

Inconstant, low-grade fever unassociated with shaking chills is recorded in 70 per cent of the cases. In only two cases is the absence of fever specifically mentioned,[4, 13] and in the descriptions of four cases no reference is made to body temperature. The average temperature is 37.8° C., although recordings as high as 39.5° C. have been made.[1]

Other complaints of a non-specific nature are weakness, lassitude, malaise and "grippy feelings" and fatigue (occasionally to the point of prostration).[8] Nausea, vomiting, and dizziness may occur,[9, 12] but it is debatable whether these symptoms are manifestations of a sepsis, or specific reaction to involvement of the cerebral arteries, as postulated by Bowers.[7]

*Specific Symptoms* (probably referable to inflammation of the temporal and other arteries).

(1) *Pain.* All patients with "temporal arteritis" have headache. It is severe, throbbing in nature, steady, and associated with hyperalgesia of the scalp. Fifty per cent of the patients suffer pain on mastication,[14] and in some this is the initial symptom. Facial swelling and redness of the skin overlying the temporal arteries, with the addition of a burning component of pain, are usually noted after the onset of headache. Immediate relief from pain and headache may follow biopsy of the inflamed temporal artery [7] and it is presumed that this follows the interruption of the afferents for pain about the vessel. Exacerbation of pain and arterial inflammation followed the extraction of three infected teeth in a case reported by Profant.[14]

Prior to the onset of the full-blown picture of temporal arteritis, there is often pain in the teeth,[1] ear,[3] jaw, zygoma,[3, 6, 13] nuchal region and occiput.[7] This symptom suggests primary involvement of other branches of the external carotid artery, notably the external and internal maxillary arteries.

The fact that in one patient pain has been noted along the course of the brachial and radial arteries and the arteries of the hands prior to the onset of temporal arteritis [9] suggests the possible polyarteritic nature of at least some cases of this disease. This is further implied by Jenning's description of a patient who suffered from pains in the thighs, knees, and ankles for nine

months prior to the onset of headache.[4] In the former case, however, the follow-up reported was inadequate to rule out periarteritis nodosa.

(2) *Ocular Symptoms.* The presenting complaint may be of ocular symptoms.[3] Indeed, it has become evident that more than a third of patients with temporal arteritis are threatened with partial or even complete loss of vision.[4, 6, 9, 12, 13] Diplopia and photophobia have been noted [4, 6]; ophthalmoscopic evidence of occlusion of the central retinal artery has been apparent in some cases,[4, 12] and one case with complete loss of vision has been reported.[18]

(3) *Cerebral Symptoms.* Four patients have presented signs suggestive of cerebral damage and encephalitis [5, 8, 10, 7] during the acute stage of the illness. Sprague and McKenzie report that their patient was considered by his intimates never to have recovered fully from his symptoms of lethargy and mental retardation. Mental sluggishness, dizziness, vomiting, dysarthria, delirium, and even coma have been described, and abnormalities in the spinal fluid colloidal gold curve were found by Schaefer and Sanders [10] in a patient with delirium and headache. In our patient acknowledged irritability and retardation of thought were noted.

(4) *Other Symptoms.* Although the average age incidence was 67, it is notable that in only two cases was the symptom of chest pain mentioned. Of these, one was our patient, and he claimed no increase in his rare anginal pains which had occurred intermittently during the past three years.

Symptoms and signs referable to the smaller visceral arteries commonly involved in periarteritis nodosa were not evident, and the hypertension frequently encountered in the latter [15] was infrequently encountered in cases of temporal arteritis.

*Course.* "Temporal arteritis" is a self-limited disease of one to 20 months' duration which may be attended by relapse,[1, 13] but which is apparently non-fatal. With the exception of visual defects secondary to arterial occlusion recovery is apparently complete and accompanied by returning pulsation in temporal arteries which completely lose all evidence of inflammation or nodularity.[14] The course of the illness seems to be unaffected by treatment, although relief has followed arterial biopsy in a few cases.[7, 9]

In patients who suffered visual loss, recovery of this function did not occur, and as noted above, at least one patient may have incurred permanent cerebral damage during the acute illness.

*Laboratory.* Tests of renal and liver function were non-contributory. A constant finding was a moderate leukocytosis ranging from 7,500 to 14,500 and averaging 12,000 to 13,000. Eosinophilia was absent.

*Bacteriology.* Because this disease is characterized by many features of a low-grade infection, and because its natural history suggests a spread of infection from the mouth or paranasal sinuses, there has been a search for a bacterial agent. Horton, Magath, and Brown isolated an actinomyces from the arterial walls of two of their cases, but this organism was considered to be a contaminant.

Dick and Freeman [6] isolated *Streptococcus viridans* from a biopsied artery, and cultured B-hemolytic streptococcus from the patient's throat. Bowers [7] cultured Gram positive cocci from his biopsied specimen, and MacDonald and Moser [2] obtained *Staphylococcus aureus* from the artery. In the latter case [2] *Streptococcus viridans* was isolated from a periapical tooth abscess.

Thus, it is evident that there is no constant bacteriological finding, and none of the postulates of Koch has been fulfilled. All blood cultures have been sterile, and routine agglutinations have been negative.

*Pathology.* Much of the dispute concerning the identity of "temporal arteritis" as a syndrome distinct from periarteritis nodosa stems from the similarity of the histological sections of the vessels involved in the two diseases. In both, the process is a panarteritis which involves all three arterial coats.

Typically, periarteritis nodosa (polyarteritis nodosa) affects only the smaller arteries (3–4 mm.) which supply the viscera, muscles, joints and subcutaneous structures, although in at least one case (studied in this clinic) the temporal artery was involved, and revealed at biopsy typical periarteritis nodosa. Grossly, the arteries are characterized by nodular, periarterial swellings which may be palpated during life.

In "temporal arteritis" the involved arteries are grossly seen as tortuous, swollen, nodular vessels with or without pulsation, with cellulitis of contiguous tissue. Evidence points to the involvement in some patients of the central artery of the retina, the occipital, radial, facial, carotid,[9] brachial, and cerebral arteries. In our patient there was radiographic evidence of calcification of the internal carotid and calcification with possible aneurysmal dilatation of the basilar artery.

Biopsies of temporal arteries have been performed in 13 of the 20 cases reported, but no patient with the disease has come to autopsy. Microscopic examination reveals a pan-arteritis which cannot be readily distinguished from that of periarteritis nodosa. The typical section reveals hypertrophy of the intima, medial necrosis associated with the formation of granulomatous tissue and the presence of foreign body giant cells, periarterial cellular infiltration, and thrombus formation. It is pointed out by Horton et al.[3] that unlike periarteritis nodosa, the microscopic picture of "temporal arteritis" reveals the frequent presence of giant cells but no aneurysmal dilatations. Eosinophilic invasion of the artery in "temporal arteritis" appears to be rare, although it is reported by Bowers [7] and is a prominent feature of our own sections. The presence of giant cells has suggested a tuberculous etiology, but no tubercles have been seen and no acid fast bacilli have been demonstrated.

The following case notes illustrate: (1) the progression of the "arteritis" as indicated by the distribution of pain from the lower half of the head to the temporal region; (2) the multiplicity of the arterial branches involved; (3) the non-specificity of the cellular reaction, suggesting non-specificity of

etiology. It is especially notable that this case while conforming clinically to the accepted picture of "temporal arteritis" displayed in the excised artery histopathological changes which have been encountered in only one other case in the literature.

## Case Report

A 68 year old married white male architect presented himself in November, 1944 (see figure 1) with a severe headache associated with prominent temporal arteries

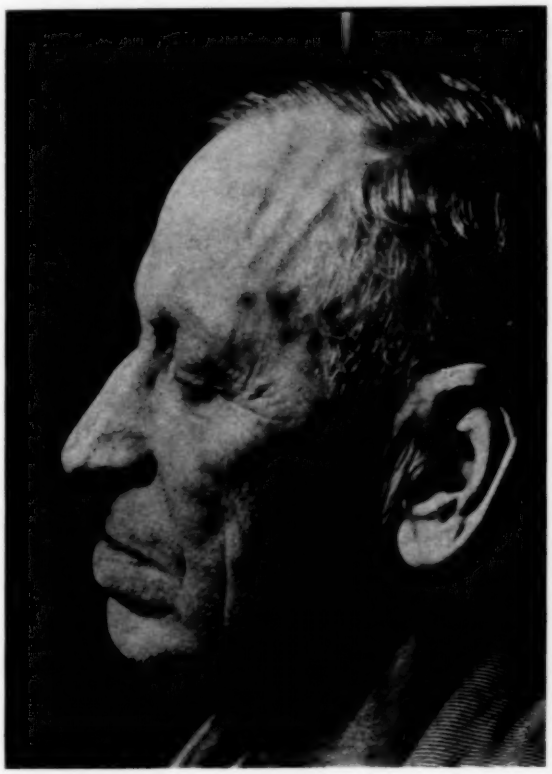

Fig. 1.

and tenderness of the skin and soft tissue in both temples and across the forehead. Two months previously (September) his appetite had become poor, he began to tire easily, and found that he had lost six pounds in weight. Shortly afterward he had a sustained pain in his left lower jaw. He noted, coincidentally, that he had a small ulcer on the gum which was irritated by his denture. However, when he removed his lower plate, the pain continued. In a few days the pain had extended to his left ear, and some days later the left temporal arteries became swollen and painful.

In three weeks from the onset of the first symptoms, he had an aching pain in both temples, across his forehead, over both left and right zygomatic regions and bilaterally in the walls of the buccal cavity. His cheeks and temples appeared slightly swollen and his masseter muscles ached when he opened his mouth. The skin over

his cheeks, temples and forehead was hyperalgesic. He said, "It felt as if I had a sunburn, and I couldn't bear to rub my fingers over it. Just to touch the hair of my temples was painful." The patient described the pain as being of two varieties, a superficial burning pain (like sunburn) and a deep aching pain, both of high intensity.

He had a pain of low intensity in his chest on exertion, his temperature was elevated, and he felt languid, lacked energy, and had no appetite. He had occasional night sweats. He could recall no headaches previous to his present illness.

Twenty years previously he had had bronchitis followed by a chronic cough, and eight years previously a "streptococcus infection" of the throat, and subsequent tonsillectomy and extraction of all of his upper teeth. With the exception of these two illnesses his general health had been good. For the past three years he had complained of substernal pain on exertion, and dyspnea on climbing 1–2 flights. These latter symptoms had not increased since the onset of the present illness.

On admission to the hospital the patient looked old and as though he had been ill for some time. The temporal arteries were large, distended, tortuous and nodular, being more prominent on the left than on the right. They were found to pulsate, and the walls were tender, thickened and firm, but compressible. They were palpable from the temporomandibular joint to the vertex of the skull, bilaterally (see illustration).

There was a tremor of the tongue and outstretched hands, and upward gaze was incomplete. Ankle jerks were absent and there was diminished vibration sense in the lower extremities. The pedal pulses were absent. Examination of the eye grounds revealed a small white patch of exudate adjacent to the superior nasal branch of the left retinal artery. Radial arteries were palpable and firm. The radial pulse was regular and the rate was 80. The heart sounds were not remarkable and the heart was not enlarged. The blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. The patient's temperature was elevated (38° C.), and his white blood cell count was 13,600. The sputum was negative for acid fast bacilli. Extensive laboratory examinations of blood, urine, stool, spinal fluid, and roentgenograms of the teeth and sinuses were non-contributory. Other roentgenograms revealed a healed minimal fibroproductive tuberculosis in the subclavicular area of the right lung, calcification of the internal carotid and basilar arteries, and arteriosclerosis of the vessels of both lower extremities. Just posterior to the dorsum sellae there was stereoscopically a spherical area of calcification which suggested an aneurysmal dilatation of the basilar artery or of the Circle of Willis. There was no roentgenographic evidence of sclerotic changes in the vascular bed of the arms. The electrocardiogram showed left axis deviation, a QRS time at upper limit of normal, and a prolonged P–R interval.

During the first six days after admission to the hospital the intensity of the pain in the head diminished rapidly. It was noted that the burning component ended before the deep aching. During the next 12 days in the hospital, the patient was almost free of pain, although the symptoms of lassitude, anorexia and weakness persisted, and night sweats occurred on several occasions. Both the pulsations which were visible in the temporal arteries and the tenderness which was present on admission disappeared. At the time of discharge from the hospital these large, distended, tortuous vessels were still firm and thickened, and pulsations could not be felt. There was no edema nor gross inflammatory reaction of adjacent tissues.

A section about 2 cm. in length of the parietal branch of the right superficial temporal artery was excised. Microscopic examination revealed the walls of the vessel to be the site of very marked inflammation throughout, with diffuse infiltration by lymphocytes and occasional polymorphonuclear leukocytes. There was as well periarteritis of the vasa vasorum. There was edema of the muscularis. The lesion was one of subacute inflammation which was characterized by innumerable lympho-

cytes, eosinophiles and fibroblastic proliferation. Giant cells were not found. The adjective "nodosa" was not applicable. However, all the elements of the vessels were uniformly and diffusely inflamed, as in a panarteritis.

The patient returned to his home on November 18, 1944. He remained free of pain and tenderness in the temporal regions, and the swelling of the arteries gradually diminished and ultimately disappeared completely. Although he appeared to have regained his health, on December 10 he had a coronary occlusion which was followed by heart failure. A second coronary occlusion on January 30 led to his death on February 1, 1945.

*Comment.* The patient here described, like others mentioned before, had initial non-specific symptoms of anorexia, weight loss, and fatigability, and at this time presented no evidence of active inflammation of the temporal arteries, i.e., headache, or painful swelling of these vessels.

Of major interest is the fact that the patient's first painful symptoms were not in the vicinity of the temporal artery, but rather in the lower jaw, an area supplied by branches of the external maxillary artery. This seems of special import in view of the fact that in at least half of the other patients with "temporal arteritis" the initial, painful, local symptoms occur in regions remote from the temporal artery. Because of the later obvious inflammation of the temporal artery and the temporal regions in these cases, it is reasonable to assume that the preceding jaw pain and stiffness, mouth stiffness, nuchal pain and tenderness, facial ache, occipital pain, and visual loss were secondary to a like acute inflammation in other branches of the carotid arteries supplying these regions. Tenderness over the carotid artery itself has been noted in another case.[9]

In this case, as in others, search for a bacterial agent by agglutination and blood cultures proved fruitless, although a leukocytosis, elevated sedimentation rate, fever and sweats were evidence for the infectious nature of the process.

The electrocardiogram in our patient (soon to die of coronary occlusion) on two occasions revealed prolongation of the P–R interval, and Q–R–S times at the upper limits of normal. Other evidence of a generalized arterial inflammation, as seen in rheumatic arteritis and periarteritis nodosa, was carefully sought for, but not elicited. Blood pressure was normal, renal function tests were normal, eosinophilia of the peripheral blood was not noted, and abdominal and muscular pains in the extremities were not evident. No evidence of heart failure was ever apparent.

The subsidence of temporal arterial swelling and the general improvement in the patient's condition prior to his coronary accident may justify the conclusion that his coronary artery disease was a coincidental occurrence in an elderly man. It may be that the coronary occlusion was related in no way to the acute inflammatory process involving the arteries of his head.

*Concept of Etiology and Pathogenesis.* The majority of patients suffering from "temporal arteritis" present evidence, by sign and symptom, of a generalized, debilitating, subacute disease. To this extent they super-

ficially resemble generalized, inflammatory diseases of blood vessels such as periarteritis and disseminated lupus. With rare exception, however, these diseases are progressive and unremitting processes which terminate fatally. It can be said with reasonable certainty that all cases of "temporal arteritis" have shown complete recovery despite the advanced ages of the persons affected, and that any residual damage is secondary to thrombosis of the branches of the carotid, and not the result of continued, active inflammation of a polyarteritic nature. Furthermore, in patients with "temporal arteritis" there is no impairment in visceral circulatory function such as has been noted in periarteritis nodosa.

It seems reasonable to postulate that the systemic symptoms of "temporal arteritis" are those of a low grade, self-limited infectious process in an elderly person of lowered resistance. There is some evidence of preceding or concomitant infection in the cases reported in the literature. In 11 of the 21 cases studied, there were signs, symptoms or other evidence of preceding or concomitant infection in the head. Seven cases presented evidence of periapical tooth or other mouth infection. One patient recovered soon after tooth extraction,[3] whereas another showed a recrudescence of symptoms following removal of three diseased teeth.[14] The patient presented in our case report had noted an ulceration of the gum at the onset of the pain in his jaw, and preceding the "temporal arteritis." This was presumably a deep infection because it was not relieved by removal of his denture. In two patients large tender cervical lymph nodes were noted during the period of arteritis [6, 11]; in another a "sore throat" believed severe enough to warrant treatment with "prontosil" was described. Roentgenological evidence of pansinusitis was discovered in still another patient.

It is presumable that "temporal arteritis" may be an allergic reaction of the arteries of the head to the bacterial products of mouth infection. Against an allergic origin, however, are: (1) the rarity of eosinophilia, (2) the advanced age of the patients affected, and (3) the localized distribution of the arteritis.

The relatively high incidence of concomitant or preceding mouth infection plus the fact that the initial pain may occur in the teeth or jaw suggests the possibility of involvement of neighboring arteriosclerotic arteries by direct extension of local infection.

Because the temporal artery is the most superficial and prominent artery of the head, its involvement in an acute inflammatory process is easily detected. It is for this reason that the name "temporal arteritis" was appended to a disease characterized by inflammation of many other branches of the common carotid artery. The facts presented make untenable the view that "temporal arteritis" is solely a disease of the temporal artery. Therefore, the name "cranial arteritis" is proposed as more appropriate for this clinical syndrome.

## Summary and Conclusions

1. The syndrome heretofore designated as "temporal arteritis" is a well-defined symptom complex occurring in aged people of the white race.

2. All but one of the patients studied presented signs and symptoms generally associated with infection, namely, anorexia, prostration, fever, sweats, weight loss, and leukocytosis; and locally, over the artery, there was heat, swelling, tenderness, redness and pain.

3. The distribution of pain and tenderness is indicative of preceding or concurrent inflammation of the arteries of the lower half of the head. In half of the patients pain over the distribution of these arteries was primary.

4. In more than half of the patients studied there was evidence of preceding or concomitant infection in the head, suggesting the possibility of spread of this infection by contiguity along the walls of branches of the external carotid artery.

5. Differentiation of "temporal arteritis" from periarteritis nodosa cannot be made from the study of histopathological sections of the diseased arteries. Although in many cases of "temporal arteritis" giant cells are found, in some eosinophilic infiltration in the absence of giant cells has occurred. Thus, there is no specificity of cellular reaction.

6. The name "temporal arteritis" is misleading, since it is probable that the disease involves other arteries of the head. Therefore, for the syndrome heretofore known as "temporal arteritis," the term "cranial arteritis" is proposed as a definitive and inclusive descriptive title.

## BIBLIOGRAPHY

1. Horton, B. T., Magath, T. B., and Brown, G. E.: Arteritis of the temporal vessels, Arch. Int. Med., 1934, liii, 400–409.
2. MacDonald, J. A., and Moser, R. H.: Periarteritis and arteritis of temporal vessels; case report, Ann. Int. Med., 1937, x, 1721–1726.
3. Horton, B. T., and Magath, T. B.: Arteritis of temporal vessels; report of seven cases, Proc. Staff Meet. Mayo Clin., 1937, xii, 548–553.
4. Jennings, G. H., and Camb, M. B.: Arteritis of temporal vessels, Lancet, 1938, ccxxxiv, 424–428.
5. Bain, C. W. C.: Arteritis of the temporal arteries, Lancet, 1938, ccxxxiv, 517.
6. Dick, G. F., and Freeman, G.: Temporal arteritis, Jr. Am. Med. Assoc., 1940, cxiv, 645–647.
7. Bowers, J. M.: Arteritis of temporal vessels; report of case, Arch. Int. Med., 1940, lxvi, 384–392.
8. Sprague, P. H., and MacKenzie, W. C.: Case of temporal arteritis (Horton-Magath syndrome), Canad. Med. Assoc. Jr., 1940, xliii, 562–564.
9. Scott, Thornton, and Maxwell, E. S.: Temporal arteritis, a case report, New Internat. Clin., 1941, ii, 220–223.
10. Schaefer, C. L., and Sanders, C. E.: Temporal arteritis, Am. Heart Jr., 1942, xxiv, 410–411.
11. Murphy, J. R.: Syndrome of temporal arteritis, New York State Jr. Med., 1942, xlii, 2236–2237.

12. JOHNSON, R. H., HARLEY, R. D., and HORTON, B. T.: Arteritis of temporal vessels associated with loss of vision; report of two cases, Am. Jr. Ophth., 1943, xxvi, 147–151.
13. SHANNON, E. W., and SOLOMON, J.: Bilateral temporal arteritis with complete loss of vision, Jr. Am. Med. Assoc., 1945, cxxvii, 647–649.
14. PROFANT, H. J.: Temporal arteritis, Ann. Otol., Rhinol., and Laryngol., 1944, liii, 308.
15. KERNOHAN, F. W., and WOLTMAN, H. W.: Periarteritis nodosa, Proc. Staff Meet. Mayo Clin., 1937, xii, 554–557.

# POLYARTERITIS NODOSA: REPORT OF 11 CASES WITH REVIEW OF RECENT LITERATURE*

By R. Bruce Logue, Major, M.C., A.U.S., F.A.C.P., and Frank Mullins, Lt., M.C., A.U.S., *Atlanta, Georgia*

Periarteritis nodosa is an obliterative, inflammatory, vascular disease involving the small arteries and arterioles. Periarteritis nodosa is an inadequate descriptive term since all coats of the vessel are involved, and since nodules may or may not be present. Polyarteritis is a more exact name. Polyarteritis is a rare condition, 350 cases having been reported up to 1942.[41] Males are involved more frequently than females, in contrast to acute disseminated lupus erythematosus. It may occur at any age, having been reported from ages 1 to 79. Fifty per cent of the patients are in the fourth and fifth decades.[8] Reports of cures are infrequent.[17, 22, 32] The mortality may be as high as 90–95 per cent, although with increasing recognition of mild or atypical cases, these figures will undoubtedly be considerably lower.

*Etiology.* The etiology is unknown. Rich and his coworkers [36a] have recently reproduced the condition in rabbits by sensitization to serum and to sulfonamides. They had previously noted the condition in patients who had received serum and sulfonamides or sulfonamides alone.[36b] Previous workers [28, 43] reproduced lesions by injection of horse serum into rabbits and others [20] by injection of macerated material from human cases. In the light of Rich's work it is probable that these lesions were of an allergic nature. Eason et al.[11] reported a case which followed the administration of scarlatinal serum to a patient with acute rheumatic fever, but did not feel that the serum was responsible. Clark and Kaplan [9] studied four patients at autopsy who had experienced serum sickness following the administration of serum for pneumonia, and two of them showed lesions of polyarteritis nodosa; however, they concluded that distinctive lesions do not follow serum disease. Cohen [10] has emphasized an irreversible allergic reaction in the vessel wall. Many workers [14, 16, 31] have commented on the frequency of association of polyarteritis nodosa and rheumatic fever or rheumatic heart disease. Selye [38] has produced arthritis similar to rheumatic fever and lesions similar to polyarteritis nodosa by the administration of desoxycorticosterone acetate to rats, suggesting a possible hormonal reaction. In the past, syphilis, streptococcal infections, toxic reactions,[21] and a filterable virus [20] have been mentioned as possible etiologic factors, but the evidence to support such theories is insufficient. It is probable that the etiology is diverse; perhaps it will be found that sensitization to serums, drugs, and infections may all play a part in its production.

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*Pathology.* The pathologic lesions are quite variable, and it is obvious that this will depend upon the vessels involved in any given case. The tissues involved in the order of frequency are kidneys (80 per cent), heart (60 per cent), liver (47 per cent), spleen, lungs, mesentery, peripheral nerves, skin and brain. It has impressed this author how often one sees involvement of the testicular arteries in addition.

The lesions are generally distributed in a patchy manner. One frequently finds the vessel wall to be normal in an area adjacent to an involved segment.

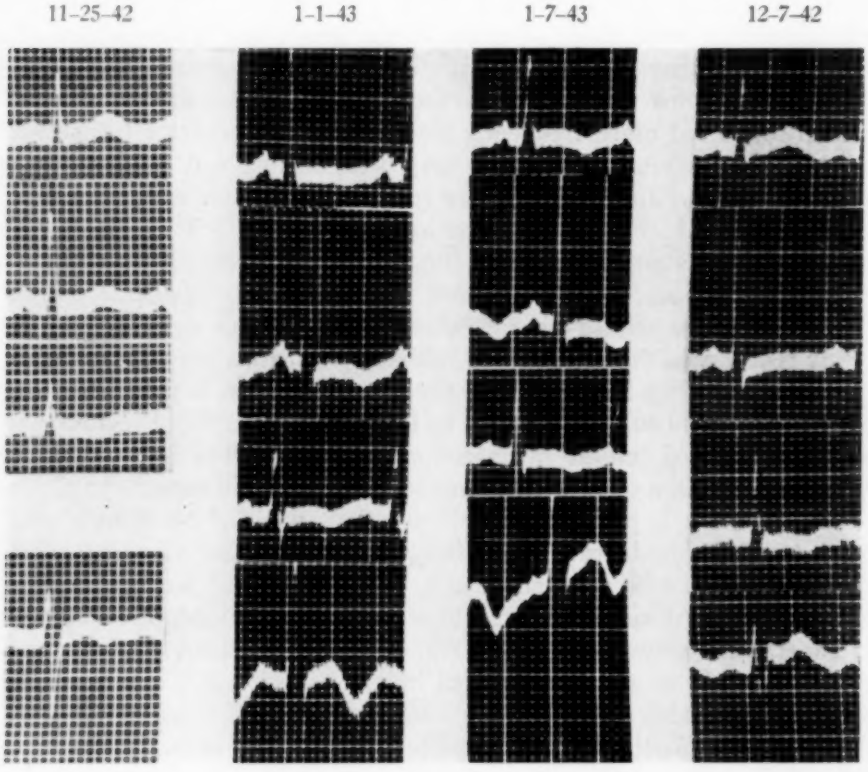


FIG. 1. *Case 6.* Note inversion of $T_4$ 11-25-42. Subsequently digitalized. T-waves became progressively inverted in all leads with slight depression of $ST_2$.

Arkin [2] arbitrarily divides the pathologic lesions into four stages: (1) degenerative; (2) acute inflammatory; (3) granulation; (4) healed. In the first stage there is hyaline degeneration of the media. In the second stage the coats become infiltrated with polymorphonuclears, eosinophiles, lymphocytes, and plasma cells. In the third stage, there is a fibroblastic proliferation with partial or total occlusion of the lumen. In the fourth stage, the lumen is greatly reduced or obliterated, and the wall is replaced by scar tissue and periarterial fibrosis. Any or all stages may be present at any given time. One not uncommonly finds the healed stage alone at autopsy.[5] The healed

lesions have no features which distinguish them from other forms of arteritis.[18] The healed stage may occur only a short while after symptoms of activity have been noted, and leads one to suspect that the change from one stage to another may be quite rapid. The frequency with which subcutaneous nodules appear and disappear over a period of a few days lends further evidence for this view. Biopsy should be performed immediately on suspected nodules, for all too often the opportunity of pathologic confirmation is lost when a few days are allowed to elapse.

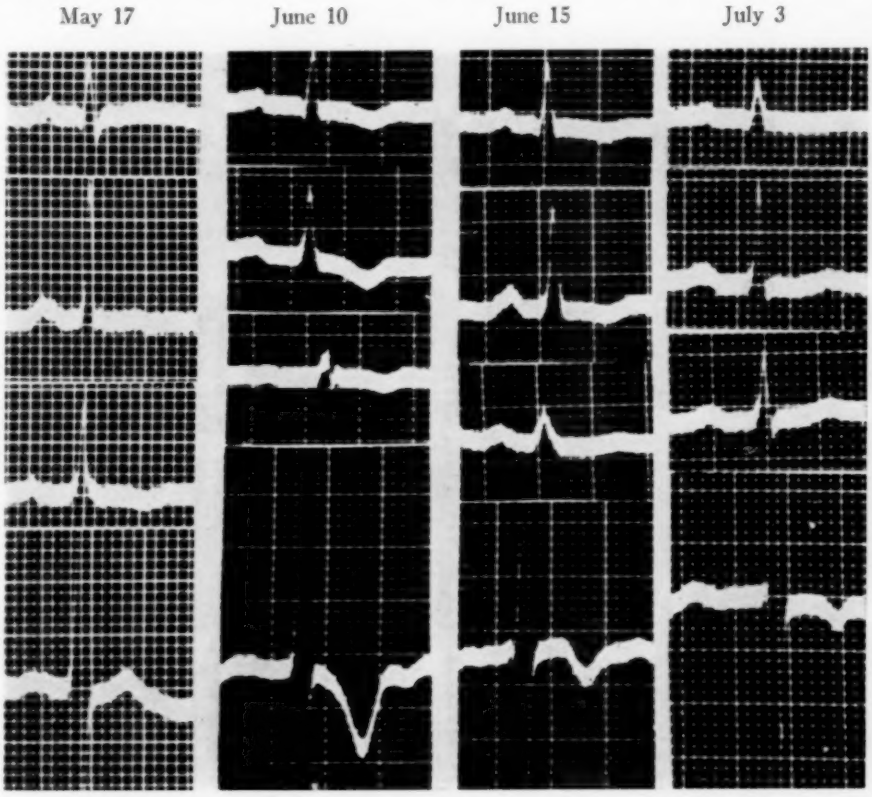


FIG. 2. *Case 8.* Note low $T_1$, diphasic $T_2$ and $T_3$ on May 17. Subsequently digitalized. T-waves became inverted in all leads with development of incomplete AV block and slight depression of ST in Leads II and IV.

All coats of the vessels are involved, although the primary involvement is thought by some observers to be in the media. As a result of the obliterative process and proliferation of the intima, thrombosis with infarction and areas of fibrosis may be noted in the organs involved. Aneurysmal dilatation and nodule formation along the arteries are common, and may give rise to the "peas in the pod" appearance, particularly in the coronary arteries. In rare instances the veins may be involved. Gross examination may at times show no abnormalities, and the diagnosis necessarily rests upon the microscopic

examination. Even so, the lesions may be missed if the condition is not suspected. Grant has stressed the importance of repeated serial sections; the diagnosis in one case could not be established until repeated sections were made.[18] The relation of polyarteritis to acute disseminated lupus erythematosus is puzzling and has been commented upon by a number of observers.[3, 46] Cases of polyarteritis clinically have shown the lesions of lupus at autopsy, and on the contrary, patients with the clinical picture of lupus

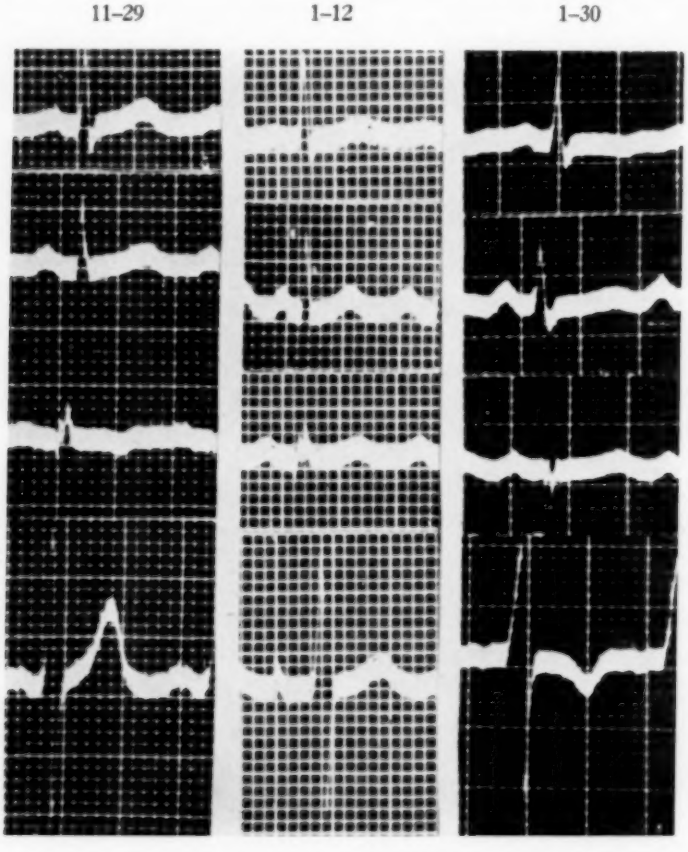


FIG. 3. *Case 5.* Note inversion of $T_1$ and $T_4$ with flattening of $T_2$ and $T_3$ on 1-30. No digitalis.

have shown polyarteritis at autopsy. Klemperer et al.[24] have commented on diffuse collagen disease, particularly in relation to periarteritis, disseminated lupus, rheumatic fever and scleroderma.

*Symptoms.* The symptomatology may be extremely variable and depends upon the tissues involved. It is common for several systems to be affected. Emerson et al.[12] have emphasized the changing character of the symptoms. The symptoms of 177 cases reported in the English literature are tabulated in table 1. Various syndromes such as chlorotic marasmus,

polyneuritis, or polymyositis and severe gastrointestinal symptoms such as described by Meyer,[30] or asthma, peripheral neuritis and eosinophilia as described by Rackemann,[34] or nephritis, anemia, and peripheral neuritis as described by Brinkman [7] have been reported. Spiegel [40] commented on the

TABLE I

Symptoms of Polyarteritis Nodosa—177 cases (modified after Harris, W. A., Lynch, G. W., and O'Hare, J. P.[19])

| | |
|---|---|
| Fever | 81% |
| Leukocytosis | 73% |
| Albuminuria | 65% |
| Abdominal pain | 56% |
| Hypertension | 53% |
| Edema | 49% |
| Neuritis | 49% |
| Hematuria | 48% |
| Rapid onset | 45% |
| Weakness | 45% |
| Loss of weight | 44% |
| Dyspnea | 40% |
| Cough | 36% |
| Emaciation | 34% |
| Sensory involvement | 34% |
| Arthritis | 34% |
| Vomiting | 33% |
| Eosinophilia (4% plus) | 33% |
| Purpura or petechiae | 27% |
| Headache | 26% |
| Visual disturbances | 23% |
| Nodules | 23% |
| Nausea | 21% |
| History of allergy | 21% |
| Atrophy | 20% |
| Cyanosis | 20% |
| Pain in chest on pressure | 17% |
| Icterus | 12% |
| Convulsions | 11% |
| Positive serologic reaction | 8% |
| Vertigo | 5% |
| Other skin eruption in absence of purpura | 4% |

Other Symptoms in 76 Cases

| | |
|---|---|
| Anemia | 48% |
| Tachycardia | 48% |
| Central nervous system involvement | 26% |
| Muscle soreness | 26% |
| Coma | 21% |
| Uremia | 13% |
| Hematemesis or bloody stools | 18% |
| Adenopathy | 11% |
| Chills | 8% |
| Diarrhea | 6% |
| Hemoptysis | 1% |

disproportion between the number and intensity of symptoms, and the disease assumed to be their cause. Fever, loss of weight, weakness, anorexia, and tachycardia are common constitutional manifestations. In the later stages of the disease, emaciation and cachexia may be striking. The disease usually extends over a period of many months, and at times years. Reports of cures

following the administration of sulfonamides or other drugs should be viewed critically, since spontaneous remission for long periods of time or even spontaneous cures have been noted.

Renal involvement may be indicated by albuminuria which occurs in 65 per cent of the cases. Painless hematuria is at times noted, and Boyd [6a] has suggested that certain cases of so-called essential hematuria may fall into this group. Pain in the flanks may accompany hematuria and usually indicates infarction or perirenal hemorrhage. Collapse and death due to ruptured aneurysms of the interlobular arteries with the formation of large perirenal hematomata was noted in 18 cases by Boyd.[6a] The shadow cast by such a mass on roentgen-ray has been mistaken for renal tumor.[37] Acute glomerulonephritis is not uncommonly simulated. In time, symptoms of renal insufficiency may occur and uremia is a frequent terminal event. The arteries of the testicles and epididymis are not uncommonly involved and may give rise to localized pain and swelling in this region. Orchitis due to infarction is a rare complication. Scrotal pain has been reported.[16]

Symptoms of coronary insufficiency with or without associated heart failure are frequent. Myocardial infarction is rare, probably owing to the slow rate of occlusion, which allows the formation of adequate collateral circulation; however, it has been recorded.[18] Hypertension is common and occurred in 53 per cent of 177 cases. It is of particular significance when it appears during the course of illness in a suspected case. The appearance of hypertension is frequently a late phenomenon, and thus, its diagnostic value in early cases is limited. Cardiac enlargement may occur in the absence of hypertension as a result of chronic coronary insufficiency. Rarely localized nodular thickenings may be palpated along small superficial arteries. The temporal arteries may exhibit such involvement, but more commonly this manifestation is unassociated with periarteritis nodosa. The vascular changes in the retinal vessels are generally secondary to hypertension. Thrombosis of the central retinal artery,[4] transient amaurosis and bilateral optic atrophy are among conditions reported.[6b] Pericarditis and pericardial tamponade due to rupture of an aneurysm of a coronary artery have been reported.[42] The endocardium may be involved by nodule formation or inflammatory thickening.[21, 45]

In a study of 200 cases, Ketron [23] found involvement of the skin in 25 per cent. The most characteristic lesion takes the form of subcutaneous nodules. These occur singly or in crops, are usually painless, and quite transient. Rarely they may pulsate.[47] Nodules were noted in 23 per cent of 177 cases. The most common skin lesion is petechia or purpura. Vesicles, urticaria, livedo reticularis, erythema and scarlatiniform eruptions have been reported. Ulceration of the skin due to thrombosis of the cutaneous arteries may occur.[23]

Neuritis is not uncommon and follows involvement of the nutrient arteries of the nerves in which thrombosis and infarction may or may not take place. With partial occlusion of the arteries, ischemia with subsequent

paresthesias may occur. These disappear with improvement of the circulation. Involvement of single nerves in the extremities is most common. More than one nerve may be involved, but the involvement is asymmetrical, since nerves are affected individually at different times.[44] Foot drop, wrist drop, motor weakness, sensory changes and paresthesias may result. Central nervous system manifestations were noted by Foster and Malamud [15] in 65 (20 per cent) of 300 cases. Among the most common manifestations were convulsions, meningeal irritation, organic brain syndrome, hemiplegia, sluggish pupil, anisocoria, cerebellar signs, Jacksonian convulsions, facial palsy and subarachnoid hemorrhage.

Muscle pain and soreness are common. The symptoms may simulate trichiniasis.[35] Joint symptoms are frequent, and may vary from arthralgia to acutely swollen joints. Migratory polyarthritis may occur.

Abdominal pain may be a prominent symptom. It is usually poorly localized, but is perhaps more common in the epigastrium. Boyd [6c] reported abdominal pain in 50 per cent of 168 patients, and in 25 per cent the pain was epigastric. The pain may simulate acute appendicitis, typhoid fever, cholecystitis, gastric ulcer, gastric carcinoma, acute pancreatitis, tuberculous enteritis and carcinoma of the colon. The mesenteric arteries are a favorite site of involvement. Thrombosis may result in infarction of the bowel wall giving pain and occult blood in the stools. Ulcerative enterocolitis with or without bloody diarrhea may result. Peritonitis may follow rupture of the bowel wall.[14, 27, 33] Felsen [13] made a diagnosis by proctoscopic examination, which revealed the vessels as persistent linear red streaks. Laparotomy is frequently performed because of obscure abdominal pain. Seven of Spiegel's [40] 17 cases were submitted to laparotomy, and in five a preoperative diagnosis of acute appendicitis was made. Singer [39] reported two cases with abdominal complaints, one of whom underwent cholecystectomy and the other missed operation because of unexplained delirium. Allen [1] reported a case with abdominal pain and boardlike stiffness of the abdomen in which operation was performed for perforating ulcer. There were extensive adhesions between the omentum and abdominal wall. Subsequent autopsy revealed periarteritis nodosa. Emerson [12] reported a case with a pulsating mass and systolic murmur in the right upper quadrant which was due to an aneurysm of the right pancreaticoduodenal artery with the formation of a retroperitoneal hematoma.

The liver is at times enlarged and jaundice may occur.[31] Involvement of the cystic artery may give rise to symptoms of acute cholecystitis. Middleton and McCarter [31] reported a case in which diabetes mellitus developed during the course of illness and autopsy revealed extensive involvement of the pancreas and its arteries. On rare occasions the spleen may be palpable. The superficial nodes are at times enlarged.

Cough, pain in the chest, and asthma are the most common pulmonary complaints. Dyspnea is usually secondary to asthma or left heart failure. The most common pathologic findings are whitish nodules along the small

pulmonary arteries, particularly in the peribronchial region near the hilum.[25, 45] Areas of fibrosis secondary to small areas of infarction may occur and at times can be detected in roentgenograms of the chest. These findings have at times given rise to an erroneous diagnosis of tuberculosis.[25] The association of asthma and polyarteritis nodosa is of some interest, particularly in view of Rich's [36a, b] recent work on sensitivity. Rackemann and Greene [34] reported eight cases with asthma and collected 27 others from the literature. Any asthmatic with marked eosinophilia should be a suspect, and Rackemann states that asthma, numbness in the extremities and eosinophilia of more than 25 per cent indicate polyarteritis nodosa. This is particularly true in females. A careful history of allergy should be sought. This has not been a striking clinical feature, although 21 per cent of 177 cases gave such a history. It may be that this will be found more commonly if a thorough search is performed. A history of intolerance to drugs, particularly sulfonamides, should be sought. McCall and Pennock [29] were unable to correlate the vascular lesions with preceding sulfonamide therapy in a series of 10 cases.

*Laboratory Findings.* Leukocytosis with a mild shift to the left is a common finding in the active stages of the disease. Repeated search for eosinophilia should be performed, as it is an inconstant finding, and is probably related to periods of fresh activity. It is probable that the figure of 33 per cent is too small and that repeated counts would give a higher figure. Cases which have shown no eosinophilia may suddenly show a sharp rise at some time during the course of illness. Extremely high eosinophile counts may at times be noted; Rackemann [34] reported a case with 84 per cent eosinophiles. The sedimentation rate is commonly elevated. Anemia may be absent in the early stages of the disease, but it is quite common in the later stages. Hematuria and albuminuria are frequent and occurred in 48 per cent and 65 per cent of cases respectively. It is again important to have repeated urine examinations to detect transient episodes of hematuria. Krupp [26] has described findings in the urinary sediment which he considered characteristic. These consist of large amounts of albumin, red cells, red cell casts, fatty casts, and waxy casts. A positive Wassermann reaction is at times seen, and in the past has given rise to the suspicion that syphilis may play a part in the etiology. Such positive serologic tests are frequently of the nature of a biologic false positive with low titers and a subsequent return to normal over a period of time. It has been observed that these patients tolerate transfusions poorly and it is suggested that atypical agglutinins may be responsible for this as well as for the serologic reactions. Serial electrocardiograms are of considerable importance and may at times be the only indication of coronary artery involvement. Tachycardia and flattening or inversion of the T-waves are the most common findings. Roentgen-ray examination is of little help, although in rare instances small areas of fibrosis or infarction can be detected in the lungs. Diagnosis in the final analysis rests upon study of a pathologic section. Biopsy of a subcutaneous nodule

or, in its absence, muscle biopsy may establish the diagnosis. The absence of a positive biopsy by no means rules out the diagnosis.

*Course.* Polyarteritis nodosa is usually of gradual onset, but the manifestations at times appear quite suddenly. The duration is more frequently many months, or at times years. The course may be punctuated by periods of remission and relapse. Recovery may take place in 5 to 10 per cent of the cases. This rate will undoubtedly increase with more frequent diagnosis. Only three of Grant's seven cases had died after three years.[18] Death is more commonly due to congestive heart failure.[6a] Uremia and hemorrhage are other not uncommon modes of termination.

The clinical features of this disease are illustrated by the following case reports.

## Case Reports

*Case 1.* I. B., colored male, aged 34, was admitted to Grady Hospital on August 21, 1939 and died January 4, 1940. Nine months before entry he developed a migratory polyarthritis involving, at one time or another, the fingers, wrists, shoulders, elbows and ankles. The joints were acutely painful and swollen, and the attacks lasted from a few days to a week. Several weeks prior to the arthritis, he had had a painful swelling over his right testicle. During subsequent months he began to lose weight and complain of weakness. For about seven months he experienced a painful burning of the feet with occasional sharp shooting pain in the legs. There was gradual inability to use the feet and legs. Two months prior to admission he noticed a vesicular eruption over the trunk and extremities. This itched severely and was followed by scaling and pigmentation. There was progressive dyspnea on exertion for about two months and occasional paroxysmal nocturnal dyspnea. Since the onset there had been a nocturia of three to four times.

As a child he had had pertussis, chickenpox, measles and pneumonia. He had experienced two attacks of gonorrhea without complications, the last attack being in December 1938. Three ribs had been fractured two years previously.

Physical examination revealed a temperature of 100° F., pulse 112, respirations 24 and blood pressure of 156 mm. Hg systolic and 110 mm. diastolic. He appeared acutely ill and dyspneic, and complained of itching of the skin and a burning sensation in the legs. Over the trunk, back and upper arms there were numerous pigmented macular areas with some central scarring. There was a mild generalized lymphadenopathy. The retinal arteries showed an increase in the light reflex with an A–V ratio of 1 to 3, with many fine and diffuse hemorrhages around the discs and slight edema of the discs and the surrounding retina.

There were many crepitant and subcrepitant râles throughout both lung fields. The heart was slightly enlarged to the left and the apex impulse was felt in the fifth intercostal space about 10 cm. from the midsternal line. The first sound at the apex was split and was followed by a soft systolic murmur. The radial arteries were markedly sclerotic. The abdomen was distended and generally tender, but more so in the right lower quadrant. The liver was palpated 3 to 4 cm. beneath the right costal margin and was slightly tender. The patellar reflexes were hyperactive. The ankle jerks were absent bilaterally. There was diminished sensation to pin-prick. There was marked motor weakness of the muscles of both feet and legs with an inability to dorsiflex the feet. A slight foot drop was present on the right side. The extremities were wasted and the feet were edematous with tense skin. The patient complained of burning pain in the legs when stimulated.

The hemoglobin was 6.4 gm. with a red count of two million. There were 8,000

leukocytes with 83 per cent polymorphonuclears and 16 per cent lymphocytes. The urine specific gravity was 1.010 and contained 4 plus albumin, with 25–30 white blood cells per high power field and 10–20 red blood cells per high power field with 5–10 hyaline casts per low power field. The sedimentation rate was 150 mm. in one hour by the Westergren method. The value for the blood sugar was 62 mg. per cent, non-protein nitrogen 35 mg. per cent and creatinine 1.5 mg. per cent. The total protein was 6.3 gm. with 3.6 gm. albumin and 2.7 gm. globulin per 100 c.c. of blood. The spinal fluid was normal. The urine concentration test gave a maximum value of 1.012, the phenolsulfonphthalein excretion 35 per cent and urea clearance test 65 per cent. A bromsulphalein test was normal and an agglutination series was negative. Repeated blood cultures were negative. Repeated blood counts revealed marked secondary anemia with leukocyte counts which varied from normal to as high as 27,900 with a slight shift to the left and an eosinophilia of 4 per cent. Repeated urinalyses revealed albuminuria, many hyaline and granular casts and many pus cells. On January 4, 1940, the non-protein nitrogen was 60 mg. per cent and the creatinine 2.1 mg. per cent.

The patient had many and varied complaints. The temperature ranged from 99° to 103° F., and was of an irregular spiking type. The pulse ranged from 90 to 110. He complained of burning in the legs for about two weeks and following this developed thrombophlebitis of the right leg. Some strength was regained in the legs but the foot drop remained. There was frequent complaint of vague abdominal pain. Pulmonary edema occurred on one occasion, and on another there was an episode of vertigo, tinnitus, nausea, vomiting, profuse perspiration and weakness of the right side of the body for a period of 24 hours. A tender area appeared over the right third chondrosternal junction and remained for several days. After five and one-half months in the hospital he gradually became drowsy and then comatose with stertorous respirations and incontinence. He died quietly on the one hundred thirty-seventh hospital day.

*Case 6.* A second lieutenant, aged 31, was admitted to hospital December 31, 1942, complaining of pain and swelling of the hands and feet. The past history was non-contributory. He had received yellow fever vaccine in March, 1942, and was hospitalized in July, 1942 because of hepatitis, which was thought to be due to the vaccine. In October 1942 he noticed soreness of the calves of the legs. Subsequently there was diminished sensation over the dorsum of the left foot and along the anterolateral aspect of the leg. A few days later there occurred severe epigastric pain which lessened to a dull aching pain, lasting one week. He was admitted to the Station Hospital October 20, 1942. For a period of six to eight hours, he lost all sensation in the left foot. After two weeks he was returned to duty and all examinations were said to have been normal. There was recurrence of the soreness in the legs, and in addition, the ankles became red, hot and swollen. He was readmitted to the hospital and developed pain in both arms, particularly the left. The painful joints did not respond to salicylates. There was a low grade fever of 99° to 101° F. He developed numbness in the arms and legs and the brachial arteries became tender with some localized areas of swelling. There was a gradual loss of 35 pounds weight. There was anorexia, constipation, and on one occasion diarrhea. He developed a cough and nocturnal dyspnea. Upon admission to this hospital, December 31, 1943, the blood pressure was 190 mm. Hg systolic and 140 mm. diastolic. The peripheral vessels were markedly sclerotic. The retinal arterioles showed generalized constriction with increased light reflex, flame shaped hemorrhages, and a few areas of exudate. The heart was normal. The lungs contained scattered fine moist râles. There was hyperesthesia over the hands and lower legs and feet. There was a left foot drop with diminished knee jerk on the left and an absent knee jerk on the right. The left testicle was smaller than the right.

TABLE II

| Case | Age | Symptoms | Signs | Laboratory | Duration | Pathology |
|---|---|---|---|---|---|---|
| 1. M. | 34 | Migratory polyarthritis, painful swell- of rt. testicle, weakness, loss of wt., burning of feet, shooting pains in legs, inability to use legs. Vesicular eruption over body. Dyspnea, nocturia × 3–4, vague abd. pain. Pul. edema on 1 occas. Episode of vertigo, tinnitus, n. and v., with weakness of rt. side of body for 24 hr. 1 transient subacute nodule over thorax. Uremia. Hist. of urticaria, no hist. of sulfonamides. | Temp. 99 to 103, B.P. 156/110. Pigmented macular areas with central scarring, mod. ret. scl. with hemorr. and exudates. Mild generalized adenopathy. Mild enl. of l. vent., sys. m. murmur, râles in lungs. Mod. rad. scl. Liver enl. 3–4 cm. beneath c.m. Absent AK, motor weakness of legs and ft. drop, wasting extremities. | R.B.C. 2 m., Hb. 6.4 gm., W.B.C. 8,000 to 27,900, sl. shift to left, max. eosinophilia of 4%, sed. rate 150. Urine alb. 4 plus, 25 to 30 W.B.C. and 10–20 R.B.C. per HPF, 5–10 hyaline casts per LPF. Fishberg conc. 1.012. PSP 35% 1 hr., urea cl. 65%. Sp. fl. normal. Total prot. 6.3 gm., alb. 3.6, glob. 2.7. Repeated agglut. series and bl. cultures neg. NPN 35–60. | 14½ months | Periarteritis nodosa involving kidneys, heart, liver, mes. aa. Lesions were of all stages from acute to healed. |
| 2. C. M. | 32 | Rx. for syphilis 5 m. Dev. cramping pain in abd. and diarrhea following injection of Bi. 6 wks. before entrance to hosp. Freq. griping abd. pain and n. since, throbbing frontal headaches for several mo., loss of 20 lbs. No hist. of allergy or sulfonamides. | B.P. 180/120, occas. temp. of 100. Emaciated. Generalized abd. tenderness without rigidity, hyperactive peristalsis. Urticaria 1 occas. Dev. subarachnoid hemorr. following laparotomy. | R.B.C. 5 m., Hb. 60%, W.B.C. 12,500–18,900 with eosinophilia 5–12%, sed. rate 109. Bl. sugar 68, NPN 27, creatinine. Urine-albumin 2 plus, few R.B.C. Sp. fl. neg. Kahn neg. Freq. occult bl. in stools. Ict. index and agglut. series normal. PSP 35% 1 hr. Retrograde pyelography, G.I. series and barium enema normal, EKG normal. | 2½ months | Laparotomy revealed whitish nodules of the vessels of the mesentery and omentum, microscopically characteristic of periarteritis nodosa. |
| 3. C. M. | 29 | Dull aching in epigas. and mid abd. 8 mo. aggravated by food, freq. n. and v., anorexia, loss of 18 lbs. Pain in both flanks, aching in legs. Noct. dysp. Tender nodules on abd. lasting 1 wk. Antisyph. Rx. 3 mo. | B.P. 205/140. Mod. ret. scl., sys. murmur mitral. Rhonchi l. lung. Low grade fever of 100. Mild adenopathy generalized. Abd. tender, espec. over g.b. and loins. Several small nontender subcut. nodules on abd. | R.B.C. 3.9 m., Hb. 10 gm., W.B.C. 10 mo. 13,000–16,000 with 2–5% eosinophiles. Urine—alb. tr., few R.B.C., occas. gran. cast, Fishberg conc. 1.012. Bl. sugar, NPN normal. Sp. fl. Kahn 2 plus. G.A. normal. G.I. Series, G.B. series and barium enema normal. Retrograde pyelograms—double ureters and pelves. Positive benzidine test on 1 stool. | 10 months | Laparotomy revealed innumerable whitish nodules like BB shot of aa. of mesentery, stomach, pancreas, colon and g.b. Nodules extended as far as 1 inch along the aa. infiltration of all coats with polys, lymphs and eosinophiles. |
| 4. C. M. | 15 | Throbbing pains in feet after walking, 3 wks., intermittent claudication, numbness and "pins" in legs. Dull pain l. flank intermittently for 3 yrs. Paroxysmal cough 6 mo. with assoc. substernal pain, sev. attacks of asthma. Papular eruption on legs and abd. 9 mo. prior to entry. No history of sulfonamides. | B.P. 160/95, pulse 140, temp. 99–101. Thickened and tortuous, temp. aa., absent pulsations in legs, dim. temp. of ft. Excoriated papules of trunk and extrem. Rhonchi in lungs, systolic murmur at apex. | R.B.C. 5.7 m., Hb. 16 gm., W.B.C. 13,000–19,850 with 5–24% eosinophiles, sed. rate 47, NPN and sugar normal, urine neg., EKG normal. | Acute symptoms subsided after 3 mo. Pt. well 3 yrs. later except for occas. asthma. | Biopsy of temp. a. lumen filled with prolif. of fibroblasts and endothelial cells among which are scattered numerous eosinophiles and an occas. poly, some interstitial hemorr. with a few polys in adventitia. |

TABLE II—*Continued*

| Case | Age | Symptoms | Signs | Laboratory | Duration | Pathology |
|---|---|---|---|---|---|---|
| 5. W. M. | 29 | Operation for draining bronchial cyst; 2 weeks later dev. pain in upper and lower extremities, migrating polyarthritis, cramping abd. pain, edema of legs and face, neuritic pains in arms and numbness of left arm, palpitation, dyspnea and terminally severe precord. pain. Loss of 24 lbs. Subcut. nodules and purpuric eruption in region of ankles. | B.P. increased from 120/80 to 160/100, temp. 99–102, tachy. Subcut. nodules in region of ankles and purpura of ankles and forearms. Wrists and ankles red, hot, tender and swollen. Liver palpable 3–4 cm. beneath c.m. Edema of face and legs. Later dev. gallop rhythm and moist râles in lungs. | R.B.C. 2.6–4 m., Hb. 50–70%, W.B.C. 14,800–46,650 with 18 to 74% eosinophilia, sed. rate 18 (Cutler). Urine 1–4 plus, alb., many R.B.C. and W.B.C., freq. hyaline casts and gran. casts, sp. gr. 1 010. Urea clearance 86%. NPN, uric acid, chlorides, sugar, phosphorus, calcium, phosphatase and urea N normal. Platelets normal. PSP 10% in 1 hr. Icterus index 5. Kahn neg., agglut. series neg. Total prot. and A/G ratio normal. Sternal biopsy neg. Repeated bl. cultures neg. EKGs—progressive evidence of cor. insuff. | 4 months | Marked edema of lungs, heart wt. 430 gm., whitish nodules along cor. aa., liver wt. 2360 gm., aa. of heart, kidney, adr. and mesentery show a chr. oblit. arteritis with scarring of media, extensive infil. with round cells, plasma cells and eosinophiles, lumen markedly oblit., pink fibrinoid present. Chr. inflammatory reaction in myocardium similar to aa. |
| 6. W. M. | 31 | Yellow fever vaccine March 1942, hepatitis July '42. Oct. '42 calf m. soreness, hypesthesia left leg. Epigas. pain. Transient loss of sensation l. ft. Ankles red, hot and swollen. Low gr. fever. Numbness of arms and legs. Tender swellings alon brach. aa. Loss of 35 lbs. Anorexia, constip., cough, nocturnal dyspnea, orthopnea, blurring of vision. Irrational. Severe pains in arms and legs. No hist. of allergy or sulfonamides. | B.P. 190/140. Emaciated. Temp. 99–101. Hyp. neuroretinitis. Heart slightly enl., moist râles in lungs. Hypesthesia hands, legs and feet, l. ft. drop, abs. A.K. rt., dim A.K. l. Pitting edema of lower extremities, fibrill., muscle tremors, coma. | R.B.C. 3.5–4.3 m., Hb. 70–80%, W.B.C. 8,000–13,000, 7% eosinophiles 1 occas., sed. rate 45. Urea clearance 105%. PSP 35%. Fishberg conc. 1.011. Urine albumin 1–4 plus, freq. R.B.C. in cast. NPN 60. Ict. index 5. Urea N. 25, creatinine 2.7, uric acid 4.5. Serial EKGs progressive evidence of cor. insuff. with inversion of T-waves in all leads. Total prot. 6.1, A/G ratio 1.3–1. Bl. cultures and agglut. series neg. Calf muscle biopsy neg. | 5 months | Heart wt. 370 gm., whitish nodules along cor. aa., nodular thickening of the mesentery aa., rt. kidney 130 gm., l. 140 gm., yellowish wedge shaped areas of infarction, interlobar aa. markedly thickened, aa. of liver show chr. oblit. process. Rt. lung 680 gm., l. lung 840 gm. |
| 7. C. M. | 42 | Cramping epigastric pain 2 mo., throbbing pain in flanks, weakness, loss of wt., dysp. on exertion 3 wk., cough, fever, constip., nocturia × 2 for several yrs., loss of 58 lbs., irregular temp. as high as 102. Developed nontender nodules over legs and along temp. aa. Terminally dev. sudden severe pain in l. lower back radiating down l. leg causing paralysis of the leg. Known hypertension 5 yrs., unexplained fever for 1 wk. 3 mo. prior to P.I. No hist. of allergy or sulfonamides. | B.P. 198/120, temp. 102. Sl. ret. scl. Heart normal size, systolic apical murmur. Tenderness both flanks. Mod. periph. scl. Dev. transient nontender nodules pretibial region and along temp. aa. Terminally no pulsations could be felt in the l. femoral artery or aa. of legs. L. leg cold and could not be moved voluntarily. | R.B.C. 4 m., Hb. 10 gm., W.B.C. 15,000, normal diff., sed. rate 120. Kahn neg. Urine 1.021, tr. alb., occas. R.B.C., W.B.C. and hyaline cast. Repeated stools pos. for occult bl. Glucose tolerance 110, 180, 270, 280 and 220, NPN 29, total prot. 5.7, alb. 3.6, glob. 2.1. PSP 51%. Agglut. series neg. G.A. normal. G.I. series and barium enema normal. Pyelograms normal. | 5 months | Periarteritis nodosa involving heart, kidneys, adrenals, pancreas, and liver. Dissecting aneurysm of aorta extending from aortic valve to bifurc. of aorta, intimal tear in region of l. subclavian artery. Heart wt. 340 gm. Rt. kidney 140 gm., l. kidney 110 gm. |

TABLE II—*Continued*

| Case | Age | Symptoms | Signs | Laboratory | Duration | Pathology |
|---|---|---|---|---|---|---|
| 8. W. M. | 21 | Back pain radiating to scrotum. Headache, nausea and vomiting 1 mo., blurring of vision. Dev. precord. pain, paroxysmal dysp., and signs of congestive failure. Hist. of treatment for syphilis in 1941. Painful swelling of ft., ankles, knees, and fingers for 1 mo., 6 mo. prior to entry. | B.P. 190/130, hyp. neuroretinitis, marked thickening and beading of radial and brachial aa. Stupor during last week of life. Temp. 99°–101°, pulse 90–110. | R.B.C. 4.8 m.–2 m., Hb. 99–45%, W.B.C. 15,000, normal diff. Urine sp. gravity 1.006, 2.4 plus alb., occas. cast, few W.B.C. and R.B.C. NPN 38 to 86, urea N 30. Kahn neg. Total prot. 4.8 with reversal of A/G ratio. Serial EKGs—progressive evidence of cor. insuff. with inversion of T-waves in all leads. | 9 months | Healed periarteritis nodosa of kidneys, heart, pancreas, testicles and thyroid. Rt. lung 750 gm., l. lung 590 gm. Heart wt. 475 gm., irregular areas of scarring of myocardium, nodular thickening of cor. aa. Rt. kidney 100, l. 110, cortex measures 4 mm. Irreg. infil. of yellowish gray tissue through cortex and medulla. |
| 9. W. M.* | 41 | Sore throat, easy fatigability, dysp. on exert., painless hematuria, occas. precord. pain, n. and v., burning sensation in abd., orthopnea, visual disturbances, itching of skin, nontender nodule over back, cough. Known hypertension for 8 yrs. Polyuria and nocturia succeeded by oliguria. No hist. of sulfonamides or allergy. | Temp. 99–101, pulse 120, B.P. 140/100–200/120. Marked ret. scl. with exudates. Heart enlarged. Slightly tender nodular pulsating mass 2 cm. in diameter at angle of rt. scapula. Mod. peripheral scl. Râles in lungs. Terminal coma. | R.B.C. 3.95 m., Hb. 56%, W.B.C. 18,000–29,000, 4% eosinophiles, slight shift to l. Urine sp. gr. 1.007, 3 plus alb. NPN 110–165, creat. 11.3–15, $CO_2$ combining power 24, urea N 100. Venous pressure 110, circ. 20 sec., EKG L.A.D., digitalis effect with inverted T in I and IV. Bl. sugar 128. | 2¼ months | Recent hemorr. into wall of rt. cor. artery giving occlusion. Thrombosis of branches of hepatic artery, cystic a., rt. gastric a. both suprarenal aa., interlobar and interlobular aa. and testicular aa. Gran. contracted kidneys, uremic pericarditis, bronchopn., patent foramen ovale, pheochromocytoma rt. suprarenal. |
| 10. W. F. | 65 | Dysp., pedal edema, intermittent epigastric pain, swelling of abd., orthopnea, night sweats, loss of wt., nocturia × 2–4, severe generalized abd. pain 3 days, nausea. No hist. of sulfonamides or allergy. Visited clinic 7–24–31, cardiac asthma, B.P. 134/76. | B.P. 140/95. Sl. cyanosis. Temp. 98.4, pulse 110–120. Heart sl. enl., liver enl. 6 cm. beneath c.m., mild ascites. Petechiae over both legs, Enl. l. supraclavicular node. Terminal coma. | R.B.C. 3.7 m., Hb. 12.8 gm., W.B.C. 12,900–15,850, 10% eosinophiles, urine sp. gr. 1.023, alb. 2 plus. Total prot. 6.6, alb, 5.1, globulin 1.5. Kahn neg. NPN 47, sug. 102. Takata Ara reaction positive. EKG L.A.D. abs. $R_4$, low $T_1T_2$. G.b. series normal, G.I. series neg. X-ray of heart—marked cardiac enl., diffuse pul. congestion. | 1 year | Laparotomy showed enl. liver with granular appearance. Ecchymoses of small intestines. Sections of liver reveal periarteritis nodosa. |
| 11. C. M.† | 39 | Known hypertension 6 mos., n. and v., anorexia, night sweats, itching of skin and light colored stools 1 wk., fever, 2 episodes of severe epigas. pain followed by persistent abd. discomfort. No hist. of allergy or sulfonamides. | B.P. 210/160, pulse 80, temp. 99–101.8. Sl. generalized lymphadenopathy. Icteric sclerae. Ret. scl. with hemorr. and exudate, palpable liver, tenderness RUQ. Flat film of abd., diffuse density in rt. upper abd., pyelograms showed ant. displacement of rt. kidney with surrounding soft tissue mass, slight elev. of rt. diaphragm. | W.B.C. 10–26,000, icterus index 125, urine 4 plus, alb., occas. R.B.C. and W.B.C. Sed. rate 27. PSP test 60%. Kahn neg. | Still alive | Mass in region of rt. kidney removed, wt. 685 gm. Kidney and adrenal completely encased in hemorrhagic fat tissue 1–4 cm. wide. Hemorrhage outside capsule and also subcapsular. Two aa. are adj. to hemorr. Micro.—ruptured interlobar a., fibrinoid degen. of media, subacute inflamm. cell infiltration with eosinophilia. Fibrosis of media. |

* Reported previously by Wolff.[47]
† Reported through courtesy of Dr. Chester Fort and Dr. Walter Sheldon.

Patient continued to complain bitterly of pain in the arms and legs and opiates were necessary for relief. Nocturnal dyspnea was severe but responded somewhat to digitalis and salyrgan with a marked clearing of the pulmonary congestion as evidenced by roentgenogram. This improvement was only temporary and marked edema of the lower extremities appeared. There was pain in the right upper quadrant which was attributed to congestion of the liver. He complained of blurring of vision coincident to hypertensive neuroretinitis. During the last two weeks of life he was irrational, exhibited fibrillary muscle tremors, and presented the picture of uremia, dying in coma March 20, 1943, five months after onset of symptoms.

Serial electrocardiograms (figure 1) showed persistent tachycardia with evidence of progressive coronary insufficiency as shown by inversion of the T-waves in Leads II, III and IV and flattening of the T-waves in Lead I. There was a moderate anemia, the red cell count varying between 3.5 and 4.3 million with a hemoglobin of 70 to 80 per cent. The leukocyte count varied from 8,000 to 13,000. On one occasion 7 per cent eosinophiles were present, but on other occasions the differential count was normal. The sedimentation rate was 45 mm. in one hour. Repeated urinalyses showed 1–4 plus albumin with frequent red cells and hyaline casts. The phenolsulfonphthalein test showed 35 per cent excretion of the dye in one hour. On March 9, 1943, the non-protein nitrogen was 60, urea nitrogen was 25, uric acid 4.5, and creatinine 2.7 mg. per 100 c.c. The total protein 6.1 gm. per 100 c.c. with an A/G ratio of 1.3 to 1. Repeated blood cultures and agglutination tests were normal. A calf muscle biopsy was negative.

The findings in 11 cases are presented in tabular form in table 2.

## Comment

Of 11 cases of polyarteritis nodosa, 10 were male and one was female. The ages ranged from 15 to 65. The duration of the illness varied from two and one-half months to one year, with recovery in one patient who was alive and well two years later. Hypertension was present in every patient at some time during the course of the disease. Leukocytosis was noted in every case and eosinophilia was present in five patients. A diagnosis was made in each instance during life, on three occasions by laparotomy. Case 11 developed a perirenal hemorrhage and nephrectomy was performed because of a suspected neoplasm. Case 7 died of a dissecting aneurysm which was unrelated to polyarteritis, there being no evidence of such disease in the aorta. Four cases showed clinical and pathologic evidence of involvement of the coronary arteries with progressive electrocardiographic evidence of coronary insufficiency (figures 1, 2, 3). Three patients showed clinical or pathologic evidence of involvement of the testicular arteries.

## Summary

Eleven cases of polyarteritis nodosa are reported. The recent English literature is reviewed and the symptoms of 177 cases are tabulated. Serial electrocardiograms demonstrating progressive involvement of the coronary arteries in three cases are recorded. A case of apparent spontaneous cure of two years' duration is reported.

## BIBLIOGRAPHY


1. Allen, Philip D.: Periarteritis nodosa simulating an acute abdominal condition requiring operation, Arch. Surg., 1940, xl, 271–276.
2. Arkin, Aaron: A clinical and pathological study of periarteritis nodosa, Am. Jr. Path., 1930, vi, 401–426.
3. Banks, B. M.: Is there a common denominator in scleroderma, dermatomyositis, disseminated lupus erythematosus, the Libman-Sacks syndrome and polyarteritis nodosa? New England Jr. Med., 1941, ccxxv, 433–444.
4. Bernstein, Alan: Periarteritis nodosa without peripheral nodules diagnosed ante mortem, Ann. Int. Med., 1935, cxc, 317–324.
5. Blaisdell, Elton, and Porter, Joseph E.: Healed stage of periarteritis nodosa, New England Jr. Med., 1941, ccxxiv, 1087–1090.

6a. Boyd, L. J.: Periarteritis nodosa, renal and cardiac manifestations, Bull. New York Med. Coll., Flower and Fifth Avenue Hosp., 1941, iv, 176–184.

b. Boyd, L. J.: The cerebral and ocular manifestations of periarteritis nodosa, Bull. New York Med. Coll., Flower and Fifth Avenue Hosp., 1943, vi, 130–138.

c. Boyd, L. J.: Periarteritis nodosa, abdominal manifestations, Bull. New York Med. Coll., Flower and Fifth Avenue Hosp., 1941, iv, 27.

7. Brinkman: Zur Klinik der Periarteritis nodosa, München. med. Wchnschr., 1922, lxix, 703.
8. Cecil, R.: Textbook of Medicine, 5th Ed., 1941, W. B. Saunders Co., Philadelphia.
9. Clark, E., and Kaplan, B. I.: Endocardial, arterial and other mesenchymal alterations associated with serum disease in man, Arch. Path., 1937, xxxiv, 458.
10. Cohen, Milton, Kline, Benjamin, and Young, Anna May: Clinical diagnosis of periarteritis nodosa, Jr. Am. Med. Assoc., 1936, cv, 1555.
11. Eason, J., and Carpenter, G.: Treatment of acute rheumatic polyarthritis with concentrated antiscarlatinal serum, Quart. Jr. Med., 1937, xxx, 93.
12. Emerson, R. S., Schroeder, H. A., and Maynard, E. P.: Periarteritis nodosa. The clinical recognition with report of an illustrative case, Brooklyn Hospital Jr., 1939, i, 107–114.
13. Felsen, J.: Sigmoidoscopic diagnosis of periarteritis nodosa, Ann. Int. Med., 1941, xv, 251–264.
14. Finkelstein, W., and Brewnan, P. J.: Periarteritis nodosa, brief review and case report, Connecticut State Med. Jr., 1943, vii, 104–106.
15. Foster, D. B., and Malamud, N.: Periarteritis nodosa. A. Clinico-pathologic reference to the central nervous system, a preliminary report, Univ. Hosp. Bull., Ann Arbor, 1941, vii, 102–104.
16. Friedberg, C. K., and Gross, L.: Periarteritis nodosa (necrotizing arteritis) associated with rheumatic heart disease, Arch. Int. Med., 1934, liv, 170–198.
17. Goldman, B. A., Dickens, K. L., and Schenker, John R.: The apparent cure of periarteritis nodosa with sulfapyridine, Am. Jr. Med. Sci., 1942, cciv, 443.
18. Grant, R. T.: Observations on periarteritis nodosa, Clin. Sci., 1940, iv, 245–275.
19. Harris, W. A., Lynch, G. W., and O'Hare, J. P.: Periarteritis nodosa, Arch. Int. Med., 1939, lxiii, 1163–1182.
20. Harris, W. H.: Etiology and pathology of periarteritis nodosa, South. Med. Jr., 1926, xix, 426–430.
21. Helpern, M., and Trubek, M.: Necrotizing arteritis and subacute glomerulonephritis in gonococcus endocarditis. Toxic origin of periarteritis nodosa, Arch. Path., 1933, xv, 35–50.
22. Jones, George M., Jr.: Periarteritis nodosa with case reports, Ann. Int. Med., 1942, xvi, 920–940.
23. Ketron, Lloyd W., and Bernstein, J. C.: Cutaneous manifestations of periarteritis nodosa, Arch. Dermat. and Syph., 1939, xl, 929–944.

24. KLEMPERER, PAUL, POLLOCK, ALBON D., and BAEHR, GEORGE: Diffuse collagen disease, Jr. Am. Med. Assoc., 1942, cxix, 331–332.
25. KLINE, B. S., and YOUNG, A. M.: Cases of reversible and irreversible allergic inflammation, Jr. Allergy, 1934, xxxv, 258.
26. KRUPP, MARCUS: Urinary sediment in visceral angiitis (periarteritis nodosa, lupus erythematosus, Libman-Sacks "disease"), Arch. Int. Med., 1943, lxxi, 56–61.
27. LUND, HERBERT Z.: Periarteritis nodosa, case record presenting clinical problems, Ohio State Med. Jr., 1942, xxxviii, 244–245.
28. MASUGI, M., and SATO, Y.: Über die allergische Gewebsreaktion der Niere. Zugleich ein experimenteller Beitrag zur Pathogenese der diffusen Glomerulonephritis und der Periarteritis nodosa, Virchow's Arch. f. path. Anat., 1934, ccxciii, 615–664.
29. MCCALL, M., and PENNOCK, J. W.: Disseminated necrotizing vascularitis, toxic origin of periarteritis nodosa, Am. Jr. Med. Sci., 1943, ccvi, 652–659.
30. MEYER, P.: Ueber Periarteriitis nodosa oder multiple Aneurysmen der mittleren und kleineren Arterien, Virchow's Arch. f. path. Anat., 1878, lxxiv, 277–319.
31. MIDDLETON, W. S., and MCCARTER, J. S.: The diagnosis of periarteritis nodosa, Am. Jr. Med. Sci., 1935 cxc, 291–308.
32. MOTLEY, LYLE: Periarteritis nodosa with report of case showing unusual features and apparent recovery, Jr. Am. Med. Assoc., 1936, cvi, 898–902.
33. PAYNE, MARSHALL J.: Periarteritis nodosa, Jr. Internat. Coll. Surg., 1941, iv, 29–34.
34. RACKEMANN, F. M., and GREENE, J. F.: Periarteritis nodosa and asthma, Trans. Assoc. Am. Phys., 1939, liv, 112.
35. REIMAN, H. A., PRICE, A. H., and HUBUT, P. A.: Trichinosis and periarteritis nodosa; differential diagnosis; possible relationship, Jr. Am. Med. Assoc., 1943, cxxii, 274–279.
36a. RICH, ARNOLD, and GREGORY, JOHN E.: The experimental demonstration that periarteritis nodosa is a manifestation of hypersensitivity, Bull. Johns Hopkins Hosp., 1943, lxxii, 65–68.
b. RICH, A. R.: The rôle of hypersensitivity in periarteritis nodosa, Bull. Johns Hopkins Hosp., 1942, lxxi, 123.
37. ROLNICK, H. C., and DAVIDSOHN, I.: Involvement of the kidney in periarteritis nodosa, Urol. and Cutan. Rev., 1942, xlvi, 626–629.
38. SELYE, HANS: Hormonal production of arthritis, Jr. Am. Med. Assoc., 1944, cxiv, 201–207.
39. SINGER, HARRY A.: Periarteritis nodosa with special reference to the acute abdominal manifestations. Report of two cases, Arch. Int. Med., 1927, xxxix, 865.
40. SPIEGEL, R.: Clinical aspects of periarteritis nodosa, Arch. Int. Med., 1936, lviii, 993–1040.
41. STEEN, G. A.: Polyarteritis nodosa, Jr. Roy. Nav. Med. Serv., 1942, xxviii, 378–384.
42. VANCE, B. M., and GRAHAM, J. E.: Periarteritis nodosa complicated by fatal intrapericardial hemorrhage, Arch. Path., 1931, xii, 521–532.
43. VAUBEL, E.: Die Eiweissüberempfindlichkeit (Gewebshypergie) des Bindegewebes, etc., Beitr. z. path. Anat. u. z. allg. Path., 1932, lxxxix, 374–418.
44. WECHSLER, Q. S., and BENDER, M. D.: The neurological manifestations of periarteritis nodosa, Jr. Mt. Sinai Hosp., 1942, viii, 1071.
45. WEIR, D. R.: Polyarteritis nodosa, report of case, Am. Jr. Path., 1939, xv, 79–88.
46. WEISS, SOMA: Medical progress: Arteries: Diseases associated with inflammatory lesions of the peripheral arteries, New England Jr. Med., 1941, ccxxv, 579–584.
47. WOLFF, B. P.: Periarteritis nodosa: report of case diagnosed ante mortem, Jr. Med. Assoc. Georgia, 1942, xxxi, 394.

# SOME UNUSUAL THORACIC COMPLICATIONS OF TYPHOID AND SALMONELLA INFECTIONS *

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THE authors have had the opportunity of observing a case of typhoid empyema with bronchopleural fistula, and a case of Salmonella costal chondritis. They have also had access to the records of one case each, of the following conditions: typhoid costal osteochondritis; pure typhoid empyema; typhoid lung abscess; and Salmonella empyema. We believe that these complications are sufficiently rare to justify reporting in some detail.

## PULMONARY COMPLICATIONS OF TYPHOID FEVER

Fifty years ago the French clinicians were singularly aware of some of the pulmonary and pleural complications of typhoid fever. In 1884, Sahli [1] reported the isolation of the typhoid bacillus from the sputum, and Jehle [2] found it present in nine of 15 cases in which he examined the sputum. Bronchitis is an almost constant part of typhoid fever, often being mild and evidenced only by a more or less productive cough. Occasionally, however, the bronchitis is severe, with profuse sputum, blood streaking or even frank hemoptysis, generalized sibilant râles, dyspnea, and cyanosis.[3, 4] Such a process was difficult to distinguish from a pneumonitis or, as it was then called, congestion, which generally affected the bases posteriorly. Caussade [5] even reported a generalized pulmonary edema, from the fluid of which *B. typhosus* was obtained in pure culture. Roque and Bancel [6] obtained the bacillus six times in 16 aspirations of the lung. Bronchopneumonia was a slightly more advanced stage of the same process, characterized, in addition, by signs of patchy consolidation. There are many postmortem reports of "congestion" and bronchopneumonic foci from which the organisms were cultured.[2, 6] These foci were noted by several observers to be more hemorrhagic than those of ordinary bronchopneumonia. It would be impossible to estimate the proportion of specific to ordinary pyogenic bronchopneumonias, but certainly the latter occurred.

Lobar pneumonia was quite rare and, when it occurred, was usually suspected of being pneumococcic. This was probably true when the complication appeared after the disease was well established. The pneumococcus was often found in the sputum and rarely both this organism and the typhoid bacillus were present. Busquet [7] reported three cases which developed clinical pneumonia and had blood cultures positive for both *B. typhosus* and

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pneumococci simultaneously. Nevertheless, pure lobar typhoid pneumonia did occur. As such, the pulmonary symptoms and signs tended to dominate the picture, the abdominal findings being minimal or absent. This syndrome, which was referred to as "Pneumotyphoid," was similar to pneumococcic lobar pneumonia except for its relatively long duration and the variable presence of symptoms referable to the abdomen. Vitug and Cruz [8] have reported a case of right lower lobe consolidation in which the sputum and blood cultures were positive for *B. typhosus,* the fever having lasted for 29 days. A palpable spleen was the single abdominal abnormality, although the stools and urine were not cultured.

The occurrence of pulmonary infarction is to be expected, as a result of the frequence of thrombophlebitis in typhoid fever. Many of the early authors assumed that the presence of bloody sputum, with or without a friction rub and signs of localized consolidation, was evidence of infarction. This assumption quite possibly gave a false impression of the incidence of infarction; but rare postmortem reports testify that it was a real possibility. Robinson [9] reported a case in which, at autopsy, the artery of the right lower lobe was plugged by a thrombus. A very large abscess occupied almost the entire lobe. In addition, there was a small basal empyema and the left lung contained scattered patches of bronchopneumonia. The abscess, pleural fluid, thrombus and left lung were all positive for *B. typhosus* in pure culture. Flexner and Harris [10] had previously reported a similar case. Finley [11] and McNaughton and Rhea [12] reported the postmortem discovery of a fresh infarct of the left lower lobe, with a hemorrhagic pleural effusion positive in pure culture for *B. typhosus.*

Abscess is perhaps the rarest pulmonary complication of typhoid. Basch,[13] Chini,[14] and Harvill,[15] among others, have reported abscesses in which the organisms were cultured from the sputum. The symptomatology apparently does not differ from that of other types of abscess, although it is probably milder than in the putrid type; the prognosis, with respect to the abscess, is certainly better. The excavation of large infarcts occasionally produces a cavity, but most abscesses are probably formed by necrosis of a locally intense specific pneumonic process. Multiple abscesses have been encountered in the moribund having an overwhelming typhoid infection.

As an example of this form of pathologic lesion we would like to cite Harvill's unusual case, which was reported from the University of Michigan Hospital in 1942. On the admission of a young typhoid fever patient, the roentgenogram of the chest was negative. Several weeks later, following a small hemoptysis, a second film of the chest revealed the presence of a small abscess cavity in the periphery of the left upper lung. The sputum was positive for *B. typhosus* on culture, and concentrate examination and culture were negative for tubercle bacilli. Subsequent films showed gradual resolution of the light infiltration surrounding the cavity and the patient made a satisfactory recovery, although at the time of discharge a small pneumatocele persisted at the site of the abscess. A recent follow-up reveals that he is

working and apparently asymptomatic. The pulmonary defect was present, essentially unchanged, as late as April, 1943.

### Pleural Complications of Typhoid Fever

Before the discovery of *Bacillus typhosus* by Eberth in 1885 the French authors were remarking upon the rarity of pleurisy, while the English and German, on the contrary, were insisting on its frequency. Subsequently, typhoid pleurisy was thoroughly studied, particularly in France. Its incidence, like that of other complications varies with the epidemic as well as with the attention of the clinicians and the frequency of thoracentesis. Cantegril [16] concludes that effusion occurs in about 2 per cent of cases of typhoid fever, although less than 0.5 per cent and as high as 7.6 per cent have been reported. A form of pleurotyphoid has been described which, analogous to pneumotyphoid, is characterized by predominance of pleuritic symptoms with the early formation of rather large amounts of fluid. In such large early effusions the toxicity may be overwhelming.* Ordinarily the effusions are small and develop after the disease is well established or during its decline. A subjacent specific pneumonitis is almost always present, as shown by the presence of cough, sputum and basal râles; the râles often persist throughout the course of the pleurisy if it is not too massive to dampen them. The symptoms do not differ materially from those of ordinary pleurisy. Pain is usually present early and a friction rub can be heard at this time. The temperature, pulse, and respirations show slight increase and, after two or three days, fluid is present in moderate amounts.[11] Characteristically, the effusions are smaller than the physical signs would indicate.[16] There may be signs and symptoms of pleurisy, but no effusion. Mouriquand [3] observed a group of pseudopleurisies which had all the signs of effusion but yielded no fluid. He felt that these represented symptomless low-grade consolidation.

The pleural fluid is serofibrinous, hemorrhagic or, rarely, purulent. It contains leukocytes in varying numbers and types. Widal has stressed the presence of large endothelial cells, supposedly from the pleura. The agglutinating power against the bacilli becomes increasingly strong but is usually weaker than that of the blood. The fluid is also increasingly bactericidal [17]; this fact probably accounts for the occasional failure to culture *B. typhosus* from it, or the disappearance of the organism from later specimens. The course of this effusion is benign and its presence apparently has little or no effect upon the mortality rate. It resorbs in from a few days to a few weeks, a single aspiration often being sufficient. It was Nordmann's [18] opinion that pleurisies which occur during convalescence are very apt to be tuberculous. Other authors disagree with this opinion. The concurrence of typhoid and tuberculosis is an obvious possibility. The former could well precipitate a tuberculous effusion; cases have been reported in which both

* See Case 1.

organisms were obtained from the fluid by culture and animal inoculation, respectively.[17]

Pyogenic infections of the pleura may occur alone or with typhoid pleurisy. Empyemata containing *B. typhosus* and pneumococci, streptococci, staphylococci or *B. coli* have been observed. Macaigne [19] reported a loculated empyema; one pocket yielded thick pus which was positive for *B. typhosus;* another contained thin serosanguineous fluid from which a pure culture of *B. coli* was obtained. A few observers have found these two organisms simultaneously in the blood stream *; this association suggests a possible etiologic relationship to ulceration in the intestinal tract.

The persistence of a typhoid effusion as a pure or mixed-infection typhoid empyema, or the development of a pyogenic empyema during the course of typhoid fever causes a mortality rate which Jandl [20] estimates to be from 15 to 20 per cent. Fortunately the incidence of empyema is extremely rare. Correia Neto and Finocchiaro [21] calculate that the number of typhoid empyemata varies from 1 to 2 per cent of the reported cases of exudative pleurisy (0.04 per cent of all cases of typhoid fever). Empyemata have been treated successfully by aspiration alone, or by intercostal drainage. As in other types of pyogenic empyema, however, the mortality, as well as the morbidity rates, are probably lower when rib resection for adequate drainage has been used.

Most empyemata apparently arise as effusions, which, for some reason, perhaps the character of the underlying pulmonary disease, persist and become purulent. Massingham [22] regarded his case as being due to infarction of the lung. An occasional right-sided empyema has been observed following hepatic or subdiaphragmatic suppuration, and Montel [23] observed one on the left side following a splenic abscess. A possible etiologic mechanism may be transpleural spread from a parasternal node, diseased cartilage, or infected rib. In Lane's case [24] a 54 year old man, who had had typhoid fever 40 years previously, developed a large empyema, the pus from which was positive for *B. typhosus.* It was thought that it might have resulted from typhoid osteitis of a rib.

## Case Reports

*Case 1.* J. T., a 26 year old white man, was admitted to the University of Virginia Hospital on November 17, 1929, with complaints of chills and fever, headache and joint pains. The patient had been well until four days before admission, when he began to feel drowsy and feverish. Profuse sweats, chills, severe headache, extreme weakness, and generalized joint pains developed within the next two days. There had been no nausea, vomiting, diarrhea, abdominal pain, or epistaxis.

Physical examination on admission to the hospital revealed a well developed, well nourished young man who appeared acutely ill. The temperature was 104° F., the pulse rate 100, and the respiratory rate 24. Rose spots were present over the abdomen. There was slight tenderness in both lower quadrants of the abdomen, with slight involuntary spasm. The liver and spleen were both slightly enlarged. Examination of the chest was negative.

* See Case 2.

Laboratory studies revealed a normal urine; hemoglobin 90 per cent, with a red cell count of 4.3 million; and a white cell count of 4,900, the differential count being normal. Examination of the stool was negative. Although cultures of blood, urine, and stool were repeatedly negative for *B. typhosus,* the serum Widal agglutination was positive. A diagnosis of typhoid fever seemed justified on the basis of the clinical picture and the laboratory studies.

The patient ran the usual toxic course of typhoid fever without complications for 10 days. His temperature ranged constantly between 103 and 104° F., and his pulse rate averaged 90 to 100. On the tenth hospital day he developed a pleural effusion on the left side. Since there were neither distressing symptoms nor a change in the course of his illness, thoracentesis was deferred until five days later when his general appearance became worse and the pulse increased. At this time, December 5, 890 c.c. of thin, brownish-red, purulent fluid were removed from the left pleural space. This fluid had a specific gravity of 1.020, and microscopically showed innumerable polymorphonuclear leukocytes in each high power field. Bacteriologic studies yielded a pure culture of *B. typhosus.* During the next two days the patient became much worse, with marked prostration and a temperature of 106° F. On December 7, 500 c.c. of fluid, somewhat thicker and more purulent than that previously aspirated, were withdrawn from the left pleural space. Culture of this fluid was also positive for typhoid organisms. The surgical consultant did not advise immediate thoracostomy because the fluid, in his opinion, was still too thin. The patient's temperature rose to 106.8° F. and his pulse to 180, and, in spite of stimulants, he died on the following day. An autopsy was not performed.

*Case 2.* A. R. M., a 20 year old white man, was admitted to the University of Virginia Hospital on October 24, 1943, complaining of fluid in his right chest and of shortness of breath. He was well until six weeks previously, when he had had a gradual onset of malaise, anorexia, headache and fever. A week later he began to have dull pain in his lower abdomen. At times he was stuporous and delirious, and weakness progressed to prostration. A physician was finally called 10 days after onset. His clinical picture and a potentially polluted supply of drinking water suggested the diagnosis of typhoid fever. Four days later dyspnea and a sense of fullness in the right side of the chest developed, and examination revealed dullness in this region. On admission at this time to a community hospital, the patient's temperature was 103° F., the respirations 30, and the pulse 118. He appeared dull and apathetic; rose spots were present over the chest and abdomen, and there were signs of pleural fluid on the right side posteriorly. Examination of the abdomen was negative.

Laboratory studies revealed a white blood count of 13,000, with 91 per cent polymorphonuclear cells and a hemoglobin of 88 per cent (Sahli); urinalysis was negative except for a two plus test for albumin; the blood culture was negative; Widal agglutination was positive on two occasions; cultures of the stool were at first negative but later positive for *B. typhosus.* A roentgenogram of the chest was essentially negative, but a second one a week later showed a moderate accumulation of pleural fluid in the right base. Thoracentesis was performed on October 9, and again on October 10, and small amounts of yellowish-red, thin, foul pus were aspirated. Cultures of this pus were positive for *B. typhosus.*

The temperature pursued a septic course of from 100 to 105° F., in spite of five days of sulfadiazine treatment. After the second thoracentesis the patient developed a productive cough, which was worse when he lay on his good side; and the sputum was foul and grossly similar to the pus aspirated from the right pleural space. The downhill, septic course persisted until the patient's admission to the University of Virginia Hospital on October 24.

Physical examination revealed an acutely ill, poorly nourished white boy, with a temperature of 103° F., pulse 124, and respirations 28. Significant physical findings were limited to the right side of the chest, where there were flatness to percussion and absent breath sounds and tactile fremitus from the sixth rib posteriorly to the diaphragm. The hemoglobin was found to be 78 per cent; the red cell count was 3.8 million; and the white cell count 15,200 with 71 per cent polymorphonuclear cells. Urinalysis was negative except for 3 to 4 white blood cells per high power field. The blood Wassermann reaction was negative. A two plus benzidine test was the only abnormal finding in the stool. The blood culture was positive for *B. coli* and *B. typhosus*, but the Widal was negative. Culture of the urine was negative, but culture of the stool was positive for typhoid organisms, with a four plus agglutinating titer in a dilution of 1:6400.

Roentgenograms disclosed a massive hydropneumothorax on the right, with the right lung at least two thirds collapsed. The left lung was clear; thoracentesis soon after admission yielded 450 c.c. of rather thick, very foul, greenish-yellow pus. Smear of this pus revealed the presence of many Gram-negative bacilli and culture was positive for *B. typhosus*.

Forty-eight hours after admission to the hospital thoracostomy under local anesthesia was performed. A four centimeter segment of the eighth rib was resected in the midaxillary line and a greatly thickened pleura incised. Approximately 800 c.c. of thick, foul pus were aspirated, and a closed system of drainage was instituted. On the second postoperative day the temperature became normal and remained so until the eleventh day, when it again rose to 101° F. For the succeeding 16 days the patient was febrile, with temperature as high as 104° F. Since roentgenograms of the chest revealed rapid expansion of the lung with adequate drainage of the residual small empyema pocket, the fever was attributed to a recrudescence of the systemic infection. This impression was confirmed by the fact that the blood cultures, which had become negative after thoracostomy, again revealed the presence of *B. typhosus*. The temperature became normal again on the twenty-eighth postoperative day and remained so until a second recrudescence 10 days later. This episode lasted nine days, with a maximum temperature of 102° F. The convalescence was then uneventful until the patient's discharge 78 days after admission. There had been a rapid return of his strength and weight, and he was ambulant.

Repeated cultures of the blood, urine, feces, and wound drainage were negative for typhoid organisms before discharge; roentgenograms of the chest revealed slight pleural thickening in the costophrenic sulcus but no pleural pocket was demonstrable. The bronchopleural fistula, suspected from the history, and demonstrated by iodized oil injection of the pleural pocket during convalescence, had closed. A small catheter which was left in the sinus on discharge from the hospital was gradually shortened, and finally removed completely on February 25, 1944. The superficial defect epithelialized in a few days. At the final examination on March 18, 1944, the patient was found to be in excellent condition with no recurrence of symptoms.

## Typhoid Osteochondritis of the Ribs

Typhoid involvement of the skeletal system is confined to the long bones, to the ribs and costal cartilages, and occasionally to the spine.[25] These lesions are not common, since as late as 1926 the Mayo Clinic had observed only three cases of typhoid osteitis.[26] They usually first appear during convalescence. The chief symptom of costal chondritis is anterior chest pain, often of a pleuritic character, which is followed by a tender, indolent swelling usually over the region of the sixth to ninth cartilages: a "cool" abscess.

This may regress and even disappear, but more often it ultimately ruptures to form a chronic sinus which drains for years and is a dangerous source of typhoid organisms. There are few if any systemic symptoms, and the lesions are amenable to surgery.

*Case 3.* J. F., a 32 year old man, was admitted to the University of Michigan Hospital, August 13, 1934, with the complaint of persistence of a draining sinus of his chest wall. In June, 1933, he had had typhoid fever. During the five weeks of his illness a tender area developed on the right upper thoracic wall anteriorly. A few weeks later a fluctuant swelling arose on the right lower thoracic wall; this was incised and became a chronic sinus. In December, 1933, the upper area finally became a sinus. Both sinuses were variously treated with irrigation, curettage, and subcutaneous typhoid vaccine. Seven weeks after onset of the original illness a small, tender, painful swelling became evident on the anterior left shin, eventually disappearing a year later. The chest sinuses discharged small sequestra and continued to drain. The pus from each was positive on culture for *B. typhosus,* and the patient was placed on the typhoid carrier list of the Michigan Department of Health.

Physical examination revealed a well developed, well nourished white man. The temperature was 100° F., the pulse 90, and the blood pressure 120 mm. Hg systolic and 70 mm. diastolic. A small draining sinus was present in the center of an irregular scar over the right third costochondral region, 6 cm. to the right of the midsternal line. A larger sinus surrounded by tags of granulation tissue was found over the right costal margin 9 cm. lateral to the midline. Both drained creamy pus. The liver was palpable 1 cm. below the right costal margin, but no other abnormalities were found. Roentgenograms of the chest and studies of the right clavicle, scapula, and upper humerus revealed no pathological changes. A roentgenogram of the left tibia revealed a very faint localized area of cortical thickening on the crest at the junction of the upper two thirds. The blood Kahn reaction was negative. Cultures taken from the sinuses yielded *B. typhosus, Staphylococcus aureus,* and a non-hemolytic streptococcus. Cultures of the stool and urine were negative for organisms of the typhoid-dysentery group. Agglutinations were positive for *B. typhosus* in a dilution of 1:320, but were negative for *B. melitensis* and *B. abortus.* Biopsies from the two sinuses revealed vascular pyogenic granulation tissue without distinctive features.

On August 18, 1934, an operation was performed by Dr. John Alexander. Under nitrous oxide-oxygen anesthesia the sinus of the upper lesion was excised to the second cartilage, which appeared somewhat expanded. Since the sinus continued into the cartilage, this was removed subperichondrally into the rib and sternum. The excised cartilage contained an abscess which was full of purulent granulations. The lower lesion was similarly treated. It involved the seventh cartilage, which was resected, together with the sixth. Two small tears were made in the pleura, but the lung was kept expanded under positive pressure until these were closed. The deep tissues were built up with sutures and the skin closed without drainage. The postoperative course was completely uneventful. The temperature never exceeded 100.2° F. during the first week, and was normal thereafter. The wounds healed *per primum* and the patient was discharged September 7. He was seen as an out-patient August 25, 1936. He had had no further symptoms and the wounds had remained healed. One year after operation he was released from the carrier files of the Department of Health.

Examination by the Department of Pathology of the tissue removed at operation showed the presence of a chronic, purulent osteomyelitis, with nothing pathognomonic of typhoid infection.

## Salmonella Infections

Of the many types of Salmonella organisms the five common ones are *S. paratyphi A* and *B, S. typhi murium, S. enteriditis,* and *S. cholerae suis* (*S. suipestifer*). Infection with these organisms assumes a much more protean form than the "paratyphoid fever" of earlier writers. Three clinical types are now recognized: (1) Salmonella gastroenteritis, which is characterized by a short incubation followed by an explosive, febrile gastroenteritis. Whereas all serologic groups may produce it, *S. typhi murium* is the commonest agent. (2) Salmonella fever,[27] which is somewhat analogous to the clinical picture of typhoid fever. It is usually caused by *S. paratyphi A* and *B*. Infection with the *A* organism is marked by fever and bacteremia, but usually no enteritis, while infection with *S. paratyphi B* produces fever, enteritis, and occasionally visceral abscesses. A large spleen and rose spots may be present, but not as regularly as in typhoid fever. (3) Salmonella septicopyemia. The members of the C serologic group, particularly *S. cholerae suis,* are most often responsible for this type of infection. There is marked invasiveness (60–66 per cent of the cases have a positive blood culture) with a tendency to bone and visceral localizations. Pulmonary involvement is especially common.

*Pulmonary and Pleural Infections.* In general, the pulmonary complications of Salmonella infections are similar to those of typhoid fever, except that they are probably more numerous.[28] Most of the cases reported prior to 1930 were due to *S. paratyphi A* or *B*. The pneumonic and bronchopneumonic lesions do not have the hemorrhagic character often seen in typhoid.[29] Jameson and Signy [30] reported a fatal case of *S. paratyphi B* infection in a child. Postmortem examination revealed consolidation of the right upper lobe and the apex of the lower. *S. paratyphi B* and *B. coli* were cultured from the consolidated area and from a succulent hilar lymph node. Thimm [31] reported a case in which a paratyphoid empyema developed. A pulmonary abscess was present in the partially collapsed lung, and both the pleural pus and the sputum were positive for *S. paratyphi B*. Abram and Glynn [32] observed a patient in whom pleurisy occurred three months after "influenza." The pleural fluid was at first clear but later became purulent, and eventually required resection of a rib. *S. paratyphi B* organisms and a streptococcus were cultured from the fluid initially, and later from the pus. Bullowa [33] was one of the first to report pulmonary infection with a Salmonella organism other than *S. paratyphi A* or *B*. In a fatal case of right middle lobe pneumonia *S. suipestifer* (*S. cholerae suis*) was grown from the sputum and from fluid aspirated by postmortem puncture of the lung. There have been several reports of bronchopneumonia associated with the septicopyemic type of infection.[34, 35, 36]

*Case 4.* Mrs. F. M., a 23 year old housewife, was admitted to the University of Michigan Hospital June 3, 1943, with the complaint of "swelling of the abdomen."

She had been well and active until two years previously, when she first noticed weakness, dyspnea, and loss of weight. Following her marriage abdominal enlargement became gradually apparent. This was followed by nausea and vomiting, amenorrhea, and edema of the feet and ankles. She entered a hospital in December, 1941, where several diagnoses were entertained, but none was confirmed. Attempts at abortion were unsuccessful, and paracentesis and diuretics were employed with moderate success. In April, 1942, a diagnosis of Banti's syndrome was made and splenectomy was performed. Following this she was much improved until a respiratory infection in November, 1942, initiated pleurisy, a productive cough, and a recurrence of dyspnea. The patient stated that clear fluid was removed from both pleural cavities on several occasions. Swelling of the abdomen and of the feet and ankles recurred and persisted. There were no familial diseases and the past history was unimportant.

Physical examination revealed a fairly well developed young woman who was pale, emaciated, and dyspneic, and who coughed frequently. The temperature was 99.6° F., the pulse 124, and the respiratory rate 32. Examination of the chest elicited signs of massive effusion on the left, and minimal dullness at the right base posterolaterally. The heart was at the upper limit of normal size with a heaving impulse transmitted to the precordium. The rhythm was regular and the sounds were loud, with a third sound audible at the apex. The liver was palpable three fingers'-breadth below the right costal margin and massive ascites was present, as well as a four-plus pitting edema of the feet and legs. The blood pressure varied between 124 and 84 mm. Hg systolic and 74 and 66 mm. diastolic. The venous pressure was 245 mm. of saline. Roentgenograms of the chest showed the presence of a large pleural effusion on the left, with a small amount of fluid in the right costophrenic sinus. The hemoglobin was 97 per cent (Sahli), the red cell count 5.3 million, and the leukocyte count 12,600 with a normal differential. The blood Kahn reaction was negative. The voided urine was negative except for a one-plus albumin. A benzidine test on the stool was very weakly positive, but there was no gross blood, mucus, ova, or parasites. The serum protein determination was 6.1 grams per cent. A single direct smear of the sputum was negative for acid fast bacilli. A bromsulphalein test showed no retention of the dye at the end of 30 minutes.

Aspiration of the left pleural space yielded 750 c.c. of thin pus from which was grown a gram negative bacillus with the cultural characteristics of the Salmonella group. It was agglutinated by *S. paratyphi B* and *S. typhi murium* sera. No acid fast organisms were found on smear or culture of either sputum or pleural exudate, and the tuberculin was negative (1:10,000 Mantoux). Stool cultures were negative for organisms of the typhoid-dysentery group. The pus was largely evacuated from the empyema space by thoracentesis and the cultural findings confirmed.

A diagnosis of constrictive pericarditis had been made, but it was felt that no operative treatment for this condition could be undertaken until the empyema had been successfully treated. Accordingly, on June 24, 1943, the empyema was drained by resection of a segment of the tenth rib posterolaterally, with the insertion of a water-sealed drainage tube. The parietal pleura was quite thick; a biopsy showed it to be lined with vascular pyogenic granulation tissue. No tubercles were found but lipophages were present in the granulation tissue. In July and August heavy diuresis was produced with ammonium chloride, Mercupurin, and Salyrgan. The ascites decreased markedly but soon began to reaccumulate. Throughout September and October a salt-free diet and Mercupurin were given, and continuous gentle suction was applied to the empyema drainage tube to encourage obliteration of the space. Roentgenographic measurements revealed a normal heart size, but fluoroscopy showed a limited amplitude of pulsation, especially along the right cardiac border. On August 31, 1943, a culture from the empyema showed the presence of *B. coli, B.*

*alkaligenes*, a non-hemolytic streptococcus, and *Staphylococcus aureus*, the latter predominating. On September 6, 1943, the same organisms, with the exception of *B. coli*, were found, and, in addition, a bacillus of the Salmonella group which failed to agglutinate with specific sera. On November 11, 1943, *S. cholerae suis* (Kunzendorf var.) was identified by cultural and serological methods, and *Staphylococcus aureus* and diphtheroid organisms were present. The empyema cavity progressively decreased in size and the sinus was healed by December.

On November 17, 1943, the patient left the hospital against advice but was readmitted December 8, 1943. On December 16, 1943, 240 c.c. of pink fluid were aspirated from the right pleural space, culture of which revealed two species of nonpathogenic gram positive bacilli. Culture for acid fast bacilli was negative. On February 12, 1944, pericardiectomy was done by Dr. Cameron Haight. The heart was found to be encased in a heavy pericardial scar 1–2 mm. in thickness over the left ventricle and 3–4 mm. thick over the right. During operation the blood pressure was initially 104 mm. Hg systolic and 88 mm. diastolic. On release of the right ventricle the pulse improved and the blood pressure immediately rose to 126 mm. Hg systolic and 100 mm. diastolic; by the end of the operation one and one-half hours later the diastolic pressure had fallen to 86 mm. Hg. The pathological report of a portion of the removed pericardium was simply: "Dense hyaline scar containing lime salts—no tubercles." Convalescence was uneventful except for the development of a paranoid state. On February 20, 1944, the blood pressure was 98 mm. Hg systolic and 80 mm. diastolic, and the venous pressure was 245 mm. of saline. Her paranoid and schizoid symptoms became worse and when she was finally discharged March 15, 1944, plans were being made to commit her to a state institution.

*Chondritis.* Lindberg [37] described costal chondritis as a common sequel during the Russian typhoid-paratyphoid epidemic of 1919–1923. It was usually associated with a "paratyphoid" relapse. He clearly outlined the pathogenesis of intrachondral and perichondral abscess, with final contiguous spread to adjacent cartilages. Brock [38] reported a *S. paratyphi B* costal chondritis with intrachondral abscess, which occurred 14 years after an attack of gastroenteritis. The patient was cured by radical excision of the diseased cartilage.

*Case 5.* M. L., a 53 year old white man, was first seen at the University of Virginia Hospital, March 18, 1943, complaining of a swollen area on his right anterior chest wall. Three months previously he had first noticed a slight, non-tender swelling in the region of the fifth cartilage just to the right of the sternum. This tumor had been preceded by a severe cough from a respiratory infection which subsided after the usual course. There was no history of trauma. Gradually the swelling increased and became painful, while the skin over the area became hyperemic. There had been no spontaneous drainage, no chills, fever or sweats, and no other systemic symptoms except a loss of eight pounds in weight during the past year. The past history was negative except for influenza in 1918 and occasional mild pleuritic attacks. One brother had died of tuberculosis, but to his knowledge the patient had never had this disease. There was no history of obscure fever or severe attacks of enterocolitis.

Physical examination revealed a superficial, indurated, reddened area 8 cm. in diameter with its center over the right fifth costal cartilage. The skin had an "orange peel" appearance and no fluctuation was present. There was mild tenderness but no local heat. The temperature, pulse and respirations were normal. The general appearance was that of chronic, low-grade infection without abscess forma-

tion. A roentgenogram of the chest showed minimal fibrosis of the right pulmonary apex. Films made with a technic to demonstrate costal detail revealed no evidence of either neoplasm or infection.

The first diagnostic impression was tuberculous infection of the thoracic wall, with the cartilage as a focus. However, a malignant tumor was considered and, therefore, under local anesthesia, a small ellipse of skin and subcutaneous tissue was removed for examination. Microscopically this tissue showed only "slight chronic inflammation, but nothing specific." Since there were no signs of toxicity and no evidence of fluctuation, conservative treatment was first advised. A series of treatments with ultraviolet light over a period of one week was followed by some improvement, but very shortly the pain increased and the center of the indurated region became fluctuant. The temperature rose to 101° F., and incision and drainage seemed necessary.

On April 6, 1943, under nitrous oxide anesthesia, a transverse incision was made over the fluctuant area roughly parallel to the fifth cartilage. Twenty cubic centimeters of thick yellow pus were encountered just beneath the subcutaneous tissue. The pyogenic cavity was lined with granulations grossly resembling tuberculous tissue. A sinus led to the fifth cartilage. On exploration, this cartilage and the chondrosternal junction were found to be diseased and were removed. The granulations of the pyogenic pocket were curetted and all grossly infected tissue removed. The wound was packed open with vaseline gauze. Culture of the pus revealed the presence of *S. cholerae suis* (Kunzendorf var.). All attempts to isolate the tubercle bacillus, including inoculation of a guinea pig, were negative. Microscopic examination of the tissue revealed only "chronic granulomatous inflammation with no evidence of tuberculosis."

The patient's convalescence was uneventful and the wound healed rapidly by relatively clean granulation tissue. However, persistent drainage from a sinus leading beneath the inferior flap necessitated a second exploration six weeks later. In spite of the fact that careful examination of the adjacent cartilages at the first operation had shown no obvious involvement, the sixth and seventh cartilages were now found to be infected. These were resected and again the wound was packed open. *S. cholerae suis* was again cultivated from the pus. Healing by second intention was rapid, until only a small dimple of granulation tissue remained. Several times epithelium covered this small defect but each time a minute accumulation of subepithelial pus would necessitate incision. Finally superficial roentgen therapy was used and complete, firm healing resulted promptly. Six months after the original drainage the wound was entirely healed and has remained so.

## Summary

Five case reports of rare thoracic complications of typhoid and Salmonella infections have been presented. Two of these were cases of costal chondritis and three were cases of empyema. All except one, an empyema which terminated fatally, were successfully treated surgically.

## BIBLIOGRAPHY

1. Sahli: Quoted by Robinson.[9]
2. Jehle, L.: Ueber den Nachweis von Typhusbacillen in Sputum der Typhuskranker, Wien. klin. Wchnschr., 1902, xxv, 232.
3. Mouriquand, G.: Note sur les complications pulmonaires, observées au cours de l'epidémie de typhoïdes et d'états typhoïdes de l'hiver 1914–15 à l'hôpital temporaire Landrement-Blandan à Nancy, Lyons méd., 1915, cxxiv, 217.

4. MINET, J.: Congestions pulmonaires à bacilles paratyphiques, Bull. de l'acad. de méd., 1916, lxxv, 196.
5. CAUSSADE, G., and TARDIEU, A.: Quelques complications pulmonaires au cours et au décours de la fiévre typhoïde, Bull. et mém. Soc. méd. d. hôp. de Paris, 1930, liv, 1635.
6. ROQUE and BANCEL: Quoted by ROBINSON.[9]
7. BUSQUET: Contribution a l'étude de la pneumo-typhoïde, Rev. de méd., 1902, xxii, 167.
8. VITUG, W., and CRUZ, J. R.: Pneumotyphoid with report of a case, Jr. Philippine Islands Med. Assoc., 1931, xx, 343.
9. ROBINSON, G.: The rôle of the typhoid bacillus in the pulmonary complications of typhoid fever, Jr. Infect. Dis., 1905, ii, 498.
10. FLEXNER, S., and HARRIS, N. McL.: Typhoid infection without intestinal lesions, Bull. Johns Hopkins Hosp., 1897, viii, 259.
11. FINLEY, F. G.: Typhoid pleurisy, Canad. Med. Assoc. Jr., 1912, ii, 764.
12. MCNAUGHTON, M. W. A., and RHEA, L. J.: A report of two cases of typhoid fever which show uncommon lesions due to the *Bacillus typhosus,* Canad. Med. Assoc. Jr., 1912, ii, 795.
13. BASCH, S.: Report of a case of typhoid fever complicated by a pure typhoid pneumonia and pulmonary abscess, Med. Rec., 1915, lxxxvii, 539.
14. CHINI, V.: Abscesso pulmonare tyfico con perforazione nel cavo pleurico e pio-pneumotorace consensuale, Policlinico (sez. prat.), 1932, xxxix, 3.
15. HARVILL, T. H.: Typhoid pulmonary abscess, Jr. Am. Med. Assoc., 1942, cxix, 494.
16. CANTEGRIL, E., and RIEUNAN, G.: Les pleurésies de la fièvre typhoïde, Gaz. d. hôp., 1932, cv, 851.
17. NORDMANN, C., and BILLET, J.: Pleurésie du déclin et de la convalescence de la fièvre typhoïde, Arch. gén. de méd., 1906, xxv, 1537.
18. NORDMANN, C.: Les pleurésies dans la fièvre typhoïde, Gaz. d. hôp., 1907, lxxx, 675.
19. MACAIGNE and THÉRY: Un cas de pleurésie typhoidique, Gaz. d. hôp., 1913, lxxxvi, 2141.
20. JANDL, J.: Über Typhusempyeme, Zentralbl. f. Chir., 1937, lxiv, 254.
21. CORREIA NETO, A., and FINOCCHIARO, J.: Empiema tífico (um caso) operado e curado, An. paulist. de med. e cir., 1937, xxxiv, 545.
22. MASSINGHAM, R.: A case of pulmonary infarction complicating enteric fever, Lancet, 1927, ii, 1289.
23. MONTEL, L.: Fièvre typhoïde à bacille atypique, abscès de la rate, pleurésie purulente, mort, Ann. de méd., 1927, xxii, 489.
24. LANE, C. R. T.: Typhoid empyema forty years after enteric fever, Lancet, 1938, i, 612.
25. PARSONS, H. C.: Post-typhoid bone lesions, Johns Hopkins Hosp. Rep., 1895, v, 417.
26. FITTS, W. T., and HARTMAN, H. R.: Post-typhoid chondritis and osteomyelitis, Med. Clin. N. Am., 1926, x, 597.
27. SACHS, J., and ANTINE, W.: Salmonella infection in man. A report of five cases with autopsies in two cases and a review of the clinical aspects, Am. Jr. Med. Sci., 1944, ccviii, 633.
28. JOLTRAIN, E., and PETITJEAN, G.: Pleurésies paratyphoïdiques, Arch. de méd. et de phar. milit., 1916, lxvi, 518.
29. MALLIÉ, H.: A propos d'un cas de pleurésie paratyphoïdique, Jr. de méd. de Bordeaux, 1921, i, 245.
30. JAMESON, H. P., and SIGNY, A.: A case of paratyphoid B infection with purpura and specific bronchopneumonia, Arch. Dis. Child., 1928–1929, xxxiv, 238.
31. THIMM, A.: Ein Fall von paratyphösem Lungenabszess, Med. klin., 1931, xxvii, 1069.
32. ABRAM, J., and GLYNN, E.: Paratyphoid infections of the pleura, Lancet, 1919, ii, 283.
33. BULLOWA, J. G. M.: *Bacillus suipestifer* (hog cholera) infection of the lung, Med. Clin. N. Am., 1928, xii, 691.
34. SHAW, F. W.: An infection of man probably due to *Salmonella suipestifer,* Jr. Lab. and Clin. Med., 1926, xii, 141.

35. Wordley, E.: A case of fever probably due to *B. paratyphosus* C, Brit. Med. Jr., 1923, ii, 105.
36. Cohen, L., Fink, H., and Gray, I.: *Salmonella suipestifer* bacteremia with pericarditis, pneumonitis and pleural effusion (report of a case), Jr. Am. Med. Assoc., 1936, cvii, 331.
37. Lindberg, B. E.: Zur Pathologie der posttyphösen Rippenchondritis, Virchow's Arch. f. path. Anat., 1925, cclviii, 367.
38. Brock, R. C.: Post-typhoid chondritis with abscess formation, Brit. Jr. Surg., 1935, xxiii, 231.

# A STUDY OF ONE HUNDRED CASES WITH A POSITIVE COCCIDIOIDIN SKIN TEST *

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LATE in 1942 it became apparent to the members of the pulmonary section of an Army General Hospital which serves the southwestern part of the United States that the number of cases of so-called minimal tuberculosis was increasing. It was decided to make intracutaneous tests on all individuals with suspicious lung lesions, not only with tuberculin but also with coccidioidin. One or more coccidioidin intracutaneous tests were made on 372 patients. One hundred twenty-five of these had a positive coccidioidin test. One hundred selected cases who had a positive coccidioidin test and residual roentgenographic findings in the lungs were chosen for study. Their analysis forms the basis for this report. Aside from four fatal cases the remainder were under observation for at least three months.

The disease coccidioidomycosis has been repeatedly described in the literature.[1, 2, 3, 4, 5, 6, 7, 8, 9] For the purpose of this study, a brief summary of coccidioidomycosis is given. The earliest lesions of coccidioidomycosis have not been observed in man but can be surmised from studies on animals.[10, 11] The disease is caused by the fungus *Coccidioides immitis*. The organism is found in the soil of certain arid regions. It has also been isolated from a number of wild rodents. In this country it is found chiefly in parts of central and southern California, Arizona, New Mexico, and West Texas.[12, 13, 14, 15, 16] The organism is diphasic.[17, 18, 19] In the soil and on culture media it occurs in the form of hyphae with chlamydospores. This is the infective form of the fungus. In animal tissue the organism occurs as a spherule with a doubly refractile wall. The spherules vary in size from 10 to 60 micra. The spherules multiply by endosporulation and gain release to the tissues when the mother cell ruptures.

The usual pathological lesion is an infectious granuloma.[20] The following is an autopsy protocol on the lungs of one of our patients. The findings in the patients who died are essentially similar and one case presents the picture for all.

"The pleura at the right apex is slightly thickened and is overlaid by fibrous tags. All lobes of both lungs are moderately firm and exhibit decreased crepitus. On palpation all lobes have a slightly 'shotty' consistency. The cut surfaces are mottled purplish-pink and slightly bloody, and on close inspection in oblique light numerous pinhead sized gray, slightly raised, miliary lesions can be seen throughout all lobes. No areas of frank consolidation or cavitation are present. The bronchi and pulmonary vessels appear normal. The lymph nodes at the hilum are moderately

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enlarged. The capsules are thickened, and the cut surfaces display large, irregular, soft, greenish-gray areas.

"(Microscopic Examination) Scattered through the lungs are innumerable small granulomatous lesions each occupying the space of two to five alveoli. These separate lesions vary in structure and age. The most typical ones show a central necrotic focus with one or more small multinucleated giant cells and characteristic coccidioides organisms. The periphery of the granulomata is occupied by various types of mononuclear elements. There are numerous variations upon this picture. What are apparently the earliest stages consist of an accumulation of mononuclear cells mingled with polymorphonuclear leukocytes within a single alveolus whose walls are well preserved. Parasites may or may not be present among the infiltrating cells. Giant cells are absent in these early foci. There are small conglomerations of such lesions with well preserved alveolar septa between them. Still later the alveolar septa are destroyed. A slight amount of diffuse fibrosis appears while necrotic centers and giant cells make their appearance. The most mature lesions appear with abundant fibrosis and a partial irregular encapsulation. In addition to these lesions there are moderate amounts of protein coagulum within some alveoli together with many red cells and numerous large macrophages with vacuolated cytoplasm and small amounts of pigment. The alveolar septa are in general moderately thickened and show considerable congestion. The alveolar walls are in general surprisingly well preserved. No large abscesses or cavitations are present."

The organism gains entrance into the body through the inhalation of infected dust, or rarely through a lesion in the skin. The vast majority of infections are mild, self-limited, and involve the lung and associated mediastinal lymph nodes.

As resistance to the disease develops, antibodies appear in the blood and the lesion heals. Frequently the lesion disappears, but occasionally fibrosis sets in and a rounded or linear scar is left. In such instances a solid immunity to the disease results. Reinfection with coccidioides does not occur. In an exceptional case an abscess may form in the lung or pleura. Such a lesion may eventually heal by absorption and fibrosis, but on the other hand it may break down and the contents be discharged through a bronchus. In the latter instance, the organisms may appear in the sputum for months or years, but apparently do not cause secondary lesions. Very rarely, owing to the severity of the initial infection or to the poor resistance of the individual (dark skinned races mostly), the infection is not limited to the lung and associated lymph nodes but gains entrance into the blood stream. Following inoculation into the blood stream, no organ or tissue of the body is immune. Many of these individuals die. A few develop enough immunity to the disease to survive, although granulomata continue to make their appearance throughout the body and are slowly absorbed or form chronic abscesses. Coccidioidomycosis mimics tuberculosis very closely. However, it is important to note that superinfection type (adult type) of pulmonary tuberculosis is not characterized by hilar or mediastinal adenopathy as is coccidioidomycosis of the lungs.

Roentgenographic studies in human cases tend to corroborate the above sequence of events.[21, 22] From a roentgenographic standpoint [9] the initial lesion in coccidioidomycosis is a pneumonia-like area of increased density

in the lung of variable size and location. Shortly thereafter one or both hilar regions usually show evidence of lymph node enlargement. If the disease does not disseminate, the pneumonia-like area will regress in a period of weeks or months. Frequently this initial lesion is confused with so-called atypical or virus pneumonia. As healing takes place the lesion may disappear or remain unchanged. If not, a rounded nodular dense area or strand-like area which often extends into the hilum is left. Occasionally the nodular lesions are seen to develop a central area of lesser density which gives the lesion the appearance of a cavity. The situation can be represented schematically as follows:

Initial pneumonia-like infiltration → Complete disappearance of lesion
Initial pneumonia-like infiltration → Nodular lesions → Annular lesions
Initial pneumonia-like infiltration → Strand-like infiltrations

The most interesting and difficult problem presented by our cases is the individual who shows a very small, soft area of increased density somewhere in the lung parenchyma on roentgen examination, but is otherwise well. The lesion usually has to be differentiated from tuberculosis, although the residuals of a pneumonitis (fibrosis, healed septic abscess, bronchitis, and bronchiectasis), Boeck's sarcoid, and metastatic malignancy may cause confusion. In an effort to establish a diagnosis in these cases particular attention was paid to the history, including the relevant facts concerning activities in areas endemic for coccidioides, the physical examination, skin tests for coccidioidin and tuberculin, blood count, urinalysis, blood Kahn and Wassermann tests, sedimentation rate, sputum, study of blood for coccidioidal antibodies, and roentgenographic examination of the chest. The following is a summary of the pertinent findings:

*History.* Fifty-two patients gave a history of pulmonary symptoms following their entrance into the desert. The typical history was that of an acute illness with fever, mild chills, cough, occasional slight hemoptysis, small amounts of mucoid sputum, and chest pain. Malaise was a frequent finding and in combination with the chest pain usually persisted. These symptoms are not characteristic of any disease but when they are found in an individual shortly after his entrance into the desert they raise the suspicion of a coccidioidal infection.

*Physical Examination.* The physical examination of the chest in most instances was entirely negative. Pleurisy, pleurisy with effusion, and pneumonitis, all secondary to a coccidioidal infection, can usually be found by physical examination. In comparison with the number of individuals who show pulmonary lesions by roentgenogram they form a small group, as only eight patients presented definite findings. From this it was felt that an evaluation of the lungs cannot be made without a roentgenogram. Four patients had skin manifestations. These proved to be coccidioidal granulomata and in three the granulomata had broken down into abscesses.

*Skin Tests.* Until November 1943 the Vollmer patch test was extensively used to rule out tuberculosis. At this time it was decided to make intracutaneous tests on all individuals giving a negative patch test with tuberculin, purified protein derivative, second strength. This strength contains 0.005 mg. of purified protein derivative per dose. We found a certain percentage of individuals who gave a positive reaction to purified protein derivative who were negative to the Vollmer patch test. This is summarized in table 1. In man, infection with *Coccidioides immitis* produces a sensitiv-

TABLE I

Total Number of Vollmer Patch Tests

| | | |
|---|---|---|
| Positive | 131 | 55% |
| Negative | 107 | 45% |

Total Number of Purified Protein Derivative, Second Strength, 0.005 mg. per Dose, Skin Tests

| | | |
|---|---|---|
| Positive | 113 | 72% |
| Negative | 43 | 28% |

Negative Vollmer Patch Tests Checked by Purified Protein Derivative, Second Strength

| | |
|---|---|
| Positive | 6 |
| Negative | 5 |

Significance of Difference Between Vollmer Test and PPD No. 2:

Vollmer positive in 55%
PPD No. 2 positive in 72%
Difference 17%

Standard deviation of difference, $\sqrt{\frac{131\times107}{238}\frac{112\times43}{155}} = .0483$

Delta over sigma delta, $.17/.0483 = 3.5$

The probability of the occurrence of a deviation of 3½ sigma is .0465, or in other words the odds against such an occurrence being a chance fluctuation in sampling is 2149 to 1 (if the conditions of simple sampling are fulfilled).

ity to coccidioidin which is essentially similar to the sensitivity produced to tuberculin by infection with the tubercle bacillus. With proper precautions the coccidioidin skin test is a very reliable procedure.[12, 23, 24, 25, 26, 27, 28]

The coccidioidin for skin testing was obtained from Dr. Charles E. Smith of the Department of Public Health, Stanford University Medical School. Dr. Smith dispenses coccidioidin in a concentrated form. We use this material in a 1:100 dilution with normal saline. No preservative is added and the diluted material is kept in the icebox. Over a period of a year and a half, different batches of the diluted coccidioidin have been frequently checked by testing known negative and positive reactors.

Of 372 patients tested seven, or 1.8 per cent, had an equivocal skin reaction. By equivocal is meant a reaction in which the area of redness and swelling was between 0.2 cm. and 0.5 cm. in diameter, faintly red, with little or no swelling. Subsequent skin tests on three of these patients were negative. The other four became definitely positive. These seven patients had all been in areas endemic for coccidioides. An inconclusive skin test must

be repeated. We chose different areas of skin for later tests. With repetition we were able in every instance to establish a reliable result. By this is meant that a positive skin test was not found in any individual who had not been in areas endemic for coccidioides. Six individuals had a severe reaction from the coccidioidin. The severe reactions were similar to those occasionally seen with tuberculin, although the tendency to ulcerate is not so great. In no patient was the reaction alarming, but there were redness and swelling of the entire anterior forearm, lymphangitis, and lymphadenitis as well as a constitutional reaction, with fever up to 101° or 102° F. A few individuals with negative or equivocal reactions were tested many times. In no instance did we see a sensitivity develop to the subcutaneous injection of coccidioidin. Of the 100 cases reported, 72 were tested more than once and were repeatedly positive. All of the equivocal skin tests and the majority of the definitely positive were checked by one of us (H. D. C.) All of the patients had a positive coccidioidin skin test at some time in the course of their disease although in two instances the test became negative as the patient became desperately ill with the disseminating form of the disease. The same type of anergic reaction is seen in tuberculosis of severe degree.

*Blood Count and Urinalysis.* Blood counts and urinalyses were of no aid in differential diagnosis.

*Blood Kahn and Wassermann Tests.* Although it is not pertinent to this study, it was noted that in five individuals, seriously ill with a coccidioidal infection, the blood Kahn and Wassermann reactions or both changed from negative to positive and back to negative again when the individual improved. There was no suspicion of a syphilitic infection in these individuals.

*Sedimentation Rate.* The sedimentation rate is elevated during active stages of the disease. In this series of cases the sedimentation rate was repeatedly normal in 61 patients.

*Sputum.* *Coccidioides immitis* was obtained by culture of the sputum in nine patients. These individuals were all seriously ill with the disease. Four of the nine patients died. In two patients, coccidioides in spherule form was seen on smear of the sputum but was not obtained on culture. We do not consider a positive smear with a negative culture for coccidioides definitely indicative of infection. It is not unusual, however, to find the double contoured spherules of coccidioides by smear in pus or spinal fluid which on culture is sterile. On June 2, 1943, one of our patients had spherules in his spinal fluid by smear, and coccidioides was obtained by culture. On June 12, 1943, spherules were again seen by smear of spinal fluid which on culture showed no growth. The patient, incidentally, made a good recovery, and examination in October of 1943* was essentially negative except for minimal lung changes. Fifty-six patients had no sputum in any quantity. Two or more gastric lavages done on these patients before breakfast were completely negative for coccidioides by smear and culture. In our

* Patient left the Veterans' Facility without permission and did not return.

experience it is extremely difficult to recover the organism from the sputum of patients with coccidioides except in the early, acute stages of the disease or in the disseminating form of the disease. In addition to the search for *Coccidioides immitis* all sputa and gastric contents were examined for acid fast organisms. Two patients with upper lobe lesions and positive skin tests for coccidioidin and tuberculin were found to have acid fast organisms in their sputa. They are not included in this series of 100 cases but they do emphasize the necessity for a careful search for the tubercle bacillus under the circumstances.

*Antibodies in the Blood.* Complement fixation and precipitin antibodies for coccidioides may be found in the blood, spinal fluid, and chest fluid when present, in the active stages of the disease.[6] Any given lesion of the chest found by roentgenographic examination and meeting certain criteria which will be more fully described below may be presumed to be due to coccidioidal infection if antibodies are found. This is due to the fact that in the vast majority of instances coccidioidal infection has its origin in the lungs. This initial infection can generally be visualized by roentgenogram at least as long as antibodies are to be found. Nine patients had complement fixation or precipitin antibodies in the blood.* This figure does not represent a true picture of the incidence of antibodies in the blood because specimens were not submitted from those patients in whom the fungus was found in the sputum or from the majority of patients whose disease appeared inactive.

*Roentgenographic Findings.* Table 2 presents the cases classified as to

TABLE II

Tabulation of Residual Lesions

This chart does not tabulate the number of individual cases with specific individual lesions. It shows the number of times that the type of lesion described in the left hand column appeared in the groups of cases presented. One case may have manifested several different types of changes in the same chest at the same time.

| Group | A | B | C | D | |
|---|---|---|---|---|---|
| Type of Manifestation on Chest Film | Proved (5 Cases) | Positive Coccidioidin Negative PPD2 (15 Cases) | Most Probable (10 Cases) | Those With Positive Coccidioidin and Positive PPD2 or Positive Patch Test (66 Cases) | Total (96 Cases) |
| Pneumonia-Like Areas | 2 | — | 3 | 21 | 26 |
| Hilar Adenopathy | 3 | 7 | 6 | 25 | 41 |
| Nodular | 1 | 6 | 6 | 38 | 51 |
| Annular (Cavity) | 2 | 3 | 2 | 14 | 21 |
| Upper Lobe Infiltrations | — | — | 1 | 16 | 17 |

* The examinations were made in the laboratory of Dr. Charles E. Smith, Dept. of Public Health, Stanford University Medical School, San Francisco, California.

the major type of roentgenographic changes exhibited and presents a combination of other clinical manifestations which aid in proving the diagnosis. The roentgenographic lesions in the lungs of 34 patients were considered to be due to coccidioidomycosis. Of these, group one, which consisted of nine cases, includes the autopsy cases. These patients had the organism isolated from the sputum. The second group, 15 in number, presented a negative reaction to the tuberculin skin test using purified protein derivative, second strength. The third group has certain outstanding findings. These are mild

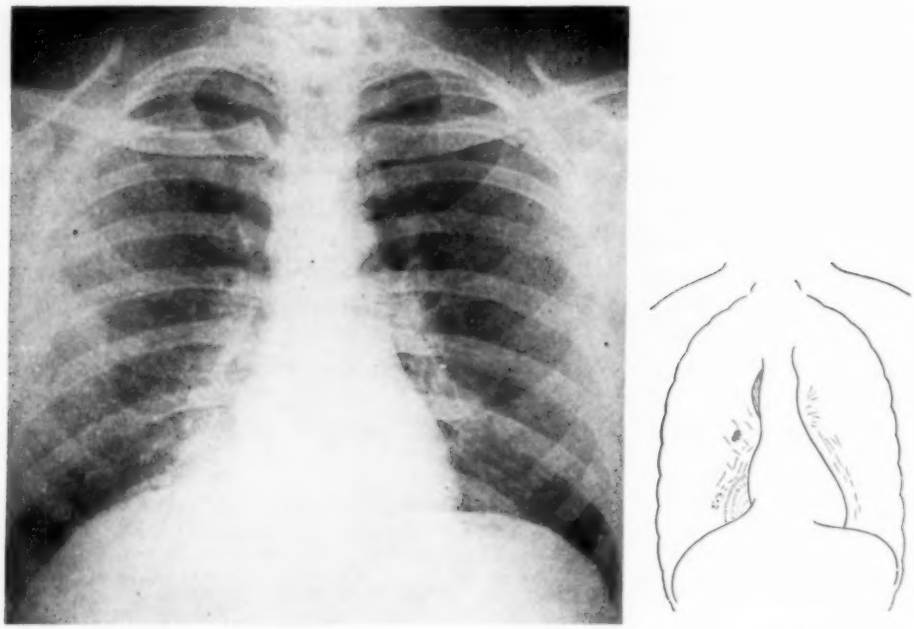

FIG. 1. Entered endemic area in May 1943. Onset of cough, dyspnea and hemoptysis early in September 1943. Coccidioidin became positive October 13, 1943, and has been positive on two tests since. Tuberculin patch test is positive. A pneumonia-like area is noted extending outward from the right cardio-phrenic angle on first observation. A slight convexity in the right upper hilar region beyond the usual course of the descending aorta is noted interpreted as a hilar node enlargement. Figure 1–A an examination 5 months following the first shows the area to have contracted to a roughly round granular appearing area of rather discrete density increase. The prominence in the upper hilum has disappeared. Intensification persists between the hilar region and the round area in the right cardiophrenic angle. This lesion is classified as a large nodular, single type of lesion.

antibody formation in the blood, the presence of fungi in a sputum examination by smear only, or the isolation of the organism from lesions other than the lungs. This group is composed of 10 cases. The other 66 cases are those individuals who in addition to a positive coccidioidin skin test, gave a positive reaction to some type of tuberculin skin test. In 36 of the 66 cases the lesions were thought to be due to coccidioidomycosis largely because of the presence of an associated hilar adenopathy or rapid regression of the lesion. This opinion was strengthened by comparing these lesions with

those of the 34 patients mentioned above. Whenever possible, former chest films were obtained. Some of these films show the development of the chest lesions as described. Examination of previous chest films frequently gives further valuable information and should always be done if such films are available. We have felt that a lung lesion, absent before but present some time after an individual was on the desert, was probably due to coccidioidomycosis even though the tuberculin skin test is positive.

The majority of the roentgenographic findings may be grouped under five major types as indicated in table 2.

1. *Pneumonia-Like Infiltrations* (figures 1 and 1-A). These areas are

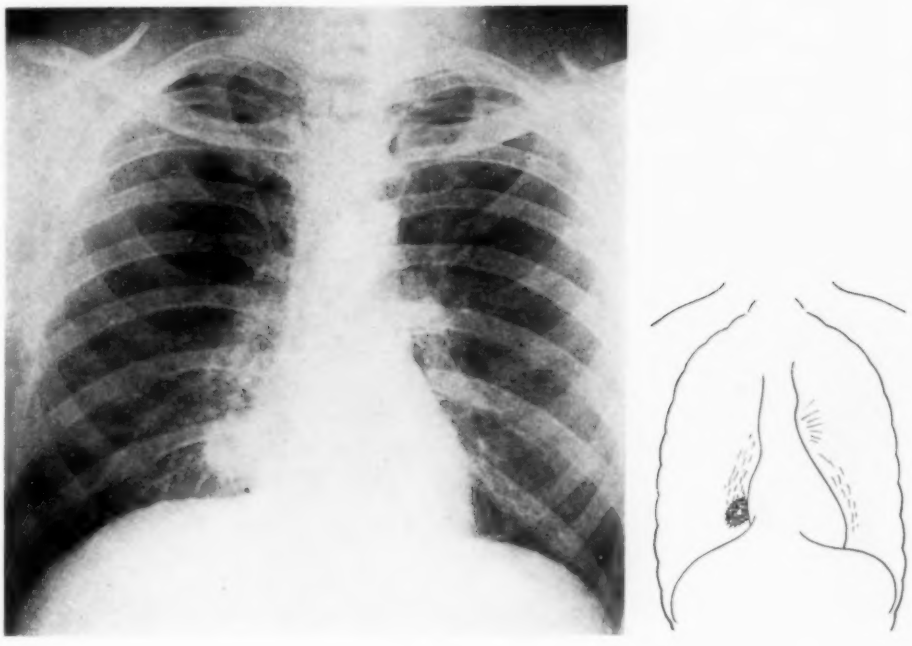

FIG. 1-A.

patchy infiltrations, centrally or peripherally situated in a portion of, or an entire lobe of a lung. The area has a variable density increase but on close examination the primary appearance is that of a group of tiny discrete nodulations intermingling with a rather soft density increase. This manifestation may be accompanied by various forms of local or generalized pleural reaction. On serial observation over a period of time the areas have frequently been noted to develop into various types of lesions such as the nodular, annular, strand-like or different combinations of all three.

2. *Tracheo-Bronchial, Mediastinal, or Hilar Adenopathy or a Combination of All* (figures 2 and 3). We have been impressed by the fact that at some time during the course of the disease changes occur in hilar shadows

of the lung which are either suggestive of, or positively identified as, significant lymph node enlargement. We believe the presence of mediastinal or hilar adenopathy to be a characteristic of pulmonary coccidioidomycosis at some time during the evolution of the pathologic process in significant infections.* These hilar shadows interpreted as enlarged lymph nodes vary in size from only a slight convexity in the lung root to large nodes as pre-

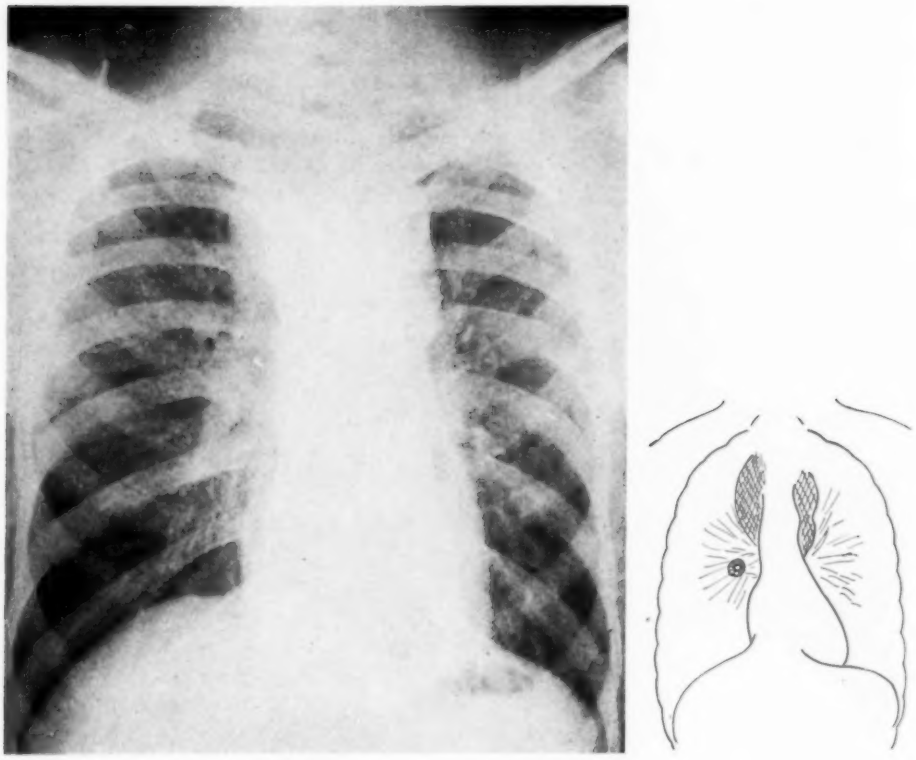

FIG. 2. First hospitalized December 22, 1943, after having been in endemic area for a period of 14 months. Presenting complaint was pain in center of chest, chills, fever and some cough. The coccidioides organism was positively identified in this patient's sputum approximately 2 months after the onset. Marked hilar or mediastinal adenopathy is noted. This adenopathy occurred to such extreme enlargement within a period of 14 days. The faintly visible lesion in the right hilar region is a type which may be easily overlooked unless careful search for it is made.

sented in figure 2. They often persist over a period of months. One patient (figure 3) had suggestive evidence of hilar adenopathy and a lung lesion that was thought to be due to coccidioidomycosis. In addition, he had chronic bronchitis which was later shown actually to be bronchiectasis. He

* The actual percentage of definite residual hilar adenopathy is 45. The per cent of definite or suggestive hilar adenopathy occurring early in the disease cannot be ascertained. By the time the importance of hilar adenopathy was appreciated many of the roentgenograms were transferred. However, the clinical impression of the authors from their studies is clearcut that hilar adenopathy is found at some stage of the disease process.

died from a brain abscess and at autopsy the hilar nodes were found to be slightly enlarged as a result of chronic inflammation. No coccidioidal granulomata were found in the nodes or in the lungs even though he had a positive coccidioidin skin test. In this instance the hilar adenopathy was not significant.

Hilar adenopathy due to coccidioides can occur with no demonstrable parenchymal lesion. If serial roentgenograms have been made on these

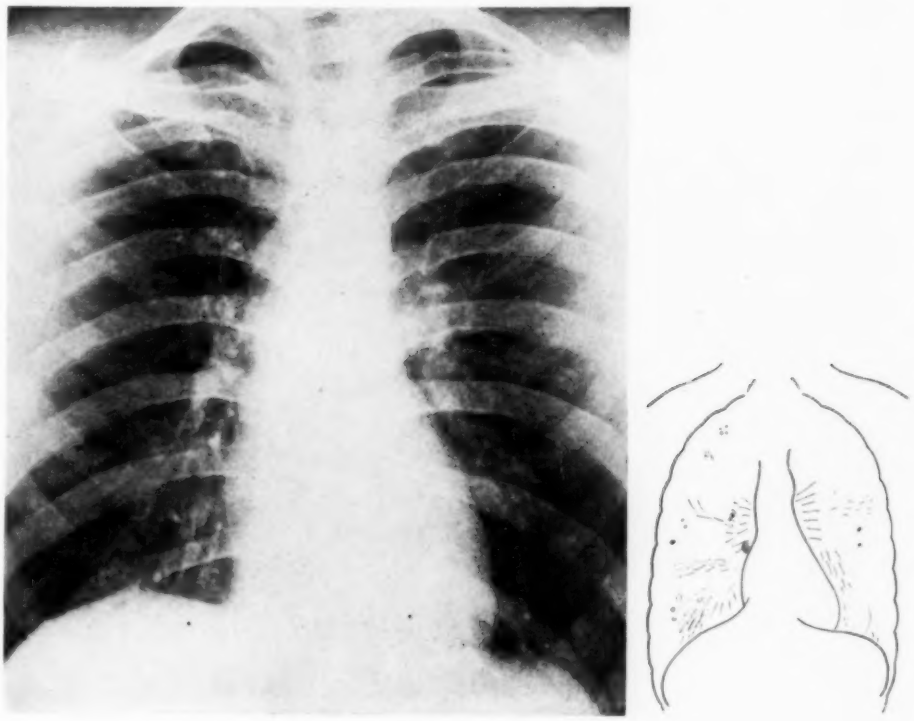

FIG. 3. This 22 year old white male entered the hospital on August 12, 1943, from Florence, Arizona, where he had been stationed since June 1943. Patient was on limited service because of chronic bronchitis. Recently had had weakness, easy fatigue, increase in cough, loss of weight, chills, sweating, small amount of yellow sputum, and pain in chest. Coccidioidin and tuberculin skin tests both positive. Bronchogram on September 15 showed bilateral tubular bronchiectasis. Following a cold, he developed right sided empyema, brain abscess, and died November 15, 1943. Autopsy confirmed these findings and showed presence of small hilar nodes without any evidence of coccidioides.

patients from the beginning of the disease lung changes can usually be demonstrated. Two of our patients who early showed lung lesions with marked enlargement of the hilar nodes were left with only the hilar adenopathy. One other patient with marked hilar adenopathy did not show a lung lesion. When this occurs node enlargement due to Boeck's sarcoid and lymphoblastoma have to be differentiated. We gave this individual the first course of the usual roentgen-ray treatment for lymphoblastoma. The

nodes did not diminish in size so that we were inclined to consider the lesion as due to coccidioidomycosis. This was especially true as there was no further evidence which indicated the presence of Boeck's sarcoid, such as the rounded areas of lesser density seen in the roentgenogram of the hands and feet, the increased serum protein, the presence of the typical granulomata of sarcoid in a biopsy of a superficial gland, or the iritis, parotitis, facial nerve syndrome.

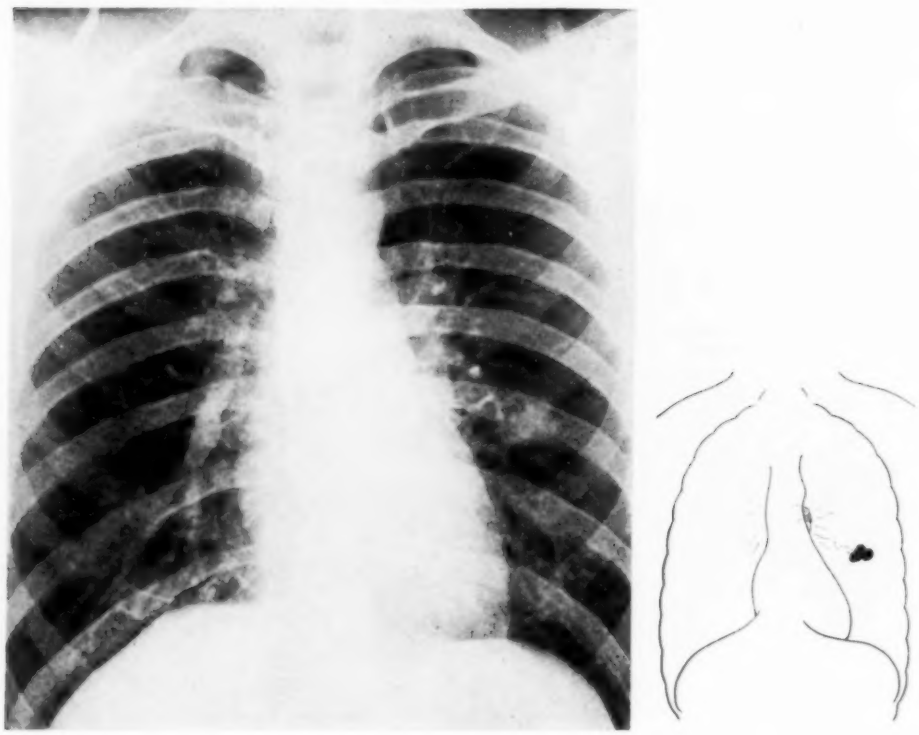

FIG. 4. Entered endemic area for coccidioidomycosis at least 6 months prior to application for Officer's Candidate School where an abnormal density was found in left lung. Patient was transferred to present hospital October 22, 1943, with a diagnosis of tuberculosis, pulmonary, left lower lobe, active, acute. On examination at this station all findings except that shown in above roentgen-ray examination were negative except a positive skin test for coccidioidomycosis and the patient had negative patch and PPD, second strength, tuberculin test.

3. *Discrete Nodular Type* (figures 4 and 5). This lesion is a round or oval area of increased density situated in the lung field usually at the periphery and predominantly in the middle and upper lung fields. The density of these areas is somewhat less than calcium and greater than the usual vascular density in the hilum of the lung. The lesions are discrete and rather sharply demarcated. They may be single or multiple.

Some of these nodular lesions have been observed to change over a period of time to ones having a central area of lessened density resembling

cavity or abscess formation. Within another lapse of time they may resume their nodular configuration and homogeneous density. The size of these areas varies from 2 to 3 mm. up to the largest observed in this series, which measures 3.5 cm. in diameter. Smith [6] has noted that these lesions occasionally may calcify. One of our patients who apparently contracted his disease many years previously, while a resident in the San Joaquin Valley of California, showed this condition (figure 6).

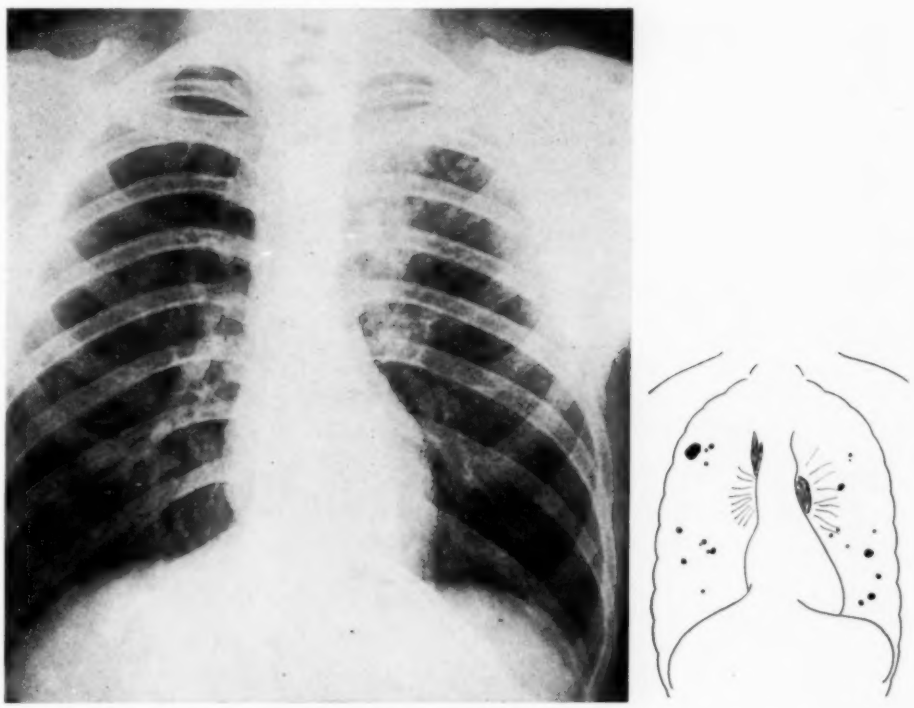

FIG. 5. Entered endemic area April 21, 1943. During September he began to tire easily, had backache and headaches. Entered local hospital October 21, 1943, transferred October 31, 1943, at which time tuberculin patch test was negative. Coccidioidin skin test was positive. No significant physical findings referable to the chest. The multiple, scattered, variable sized, round, discrete nodular areas of greater density are noted. These areas resemble the occasional so-called grape-like shadow associated with tuberculous findings. Observation of this patient's chest over a period of four months shows that these nodular areas became less dense (faded) and smaller. The patient was subsequently returned to full duty. Both single and multiple nodular types of this lesion have been observed, in sizes varying from a few mm. up to the largest, approximately 3 cm. in diameter.

4. *Annular Shadows* (Cavities, figures 7 and 7A). The predominant annular shadows observed in this series are areas of annular configuration having a relatively thick wall. As described under the nodular type these areas may change from time to time but always have a relatively thick wall which closely resembles a zone of inflammatory reaction about a focus of necrosis. There is no evidence of tissue reaction beyond the total area of involvement.

A thin-walled type of cavity has been conspicuous by its rarity in this series of cases. The one outstanding case presenting this finding is seen in figure 8. This closely resembles the pneumatocoele-like shadow described by Carter [21] and the thin-walled cavity described by Winn.[29]

5. *Upper Lobe Infiltrations* (figures 9 and 9A). This type of infiltration is confined to the upper lung field where a suggestively fine granular or poorly defined fuzzy cloudiness is present with extension of linear markings

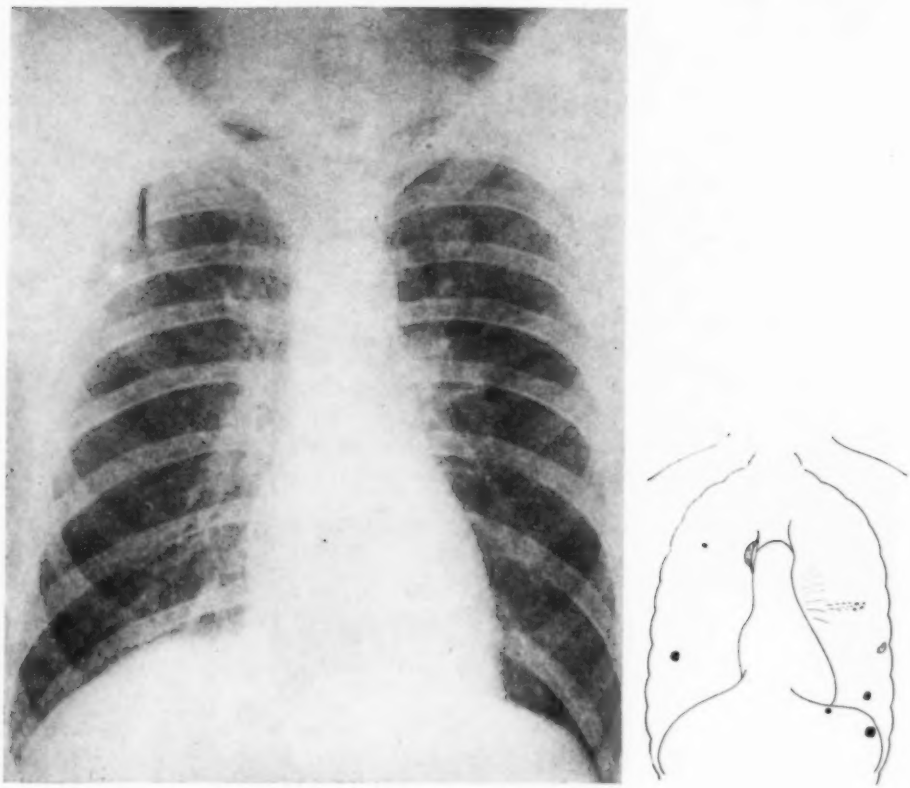

FIG. 6. Patient lived most of his life in the San Joaquin Valley of California. Chest films were made in 1942 and in 1944 and are essentially the same. The tuberculin skin test, PPD, second strength, was repeatedly negative. Coccidioidin skin test was positive. All of the nodular type lesions show internal calcifications.

into the hilum. In some cases, on close examination of these areas, very small nodular formations may be observed with an occasional area suggesting a very small cavitation.

*Roentgen-Ray Lesions in Autopsied Cases.* The different types of roentgen-ray manifestations above described and demonstrated in figures 1, 2, 4, 5, 7, 8, 9 inclusive were seen in the four patients who died and on whom autopsies were performed. All four of these cases presented roentgen-ray

findings in the chest which suggested a diffuse inflammatory process as the essential gross finding. Additional detailed evidence was as follows:

One case presented diffuse miliary nodular lesions with fuzzy linear intensification throughout both lung fields when first seen. During two months' observation these miliary lesions were seen to progress in both size and number until on an examination just prior to death there were blotchy areas present resembling confluent bronchopneumonia. These blotchy areas appeared to be a coalescence of some of

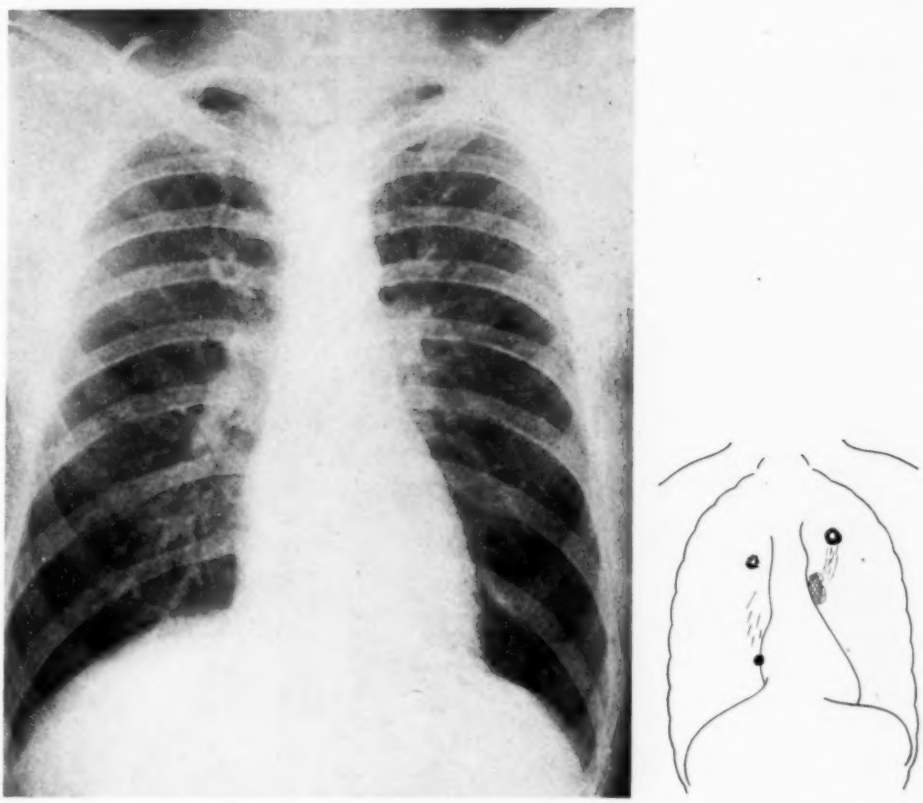

FIG. 7. Time of entrance into endemic area not definitely known. Entered Hospital in Arizona May 15, 1943. No symptomatic history. Has positive coccidioidin skin test. The round cavity or abscess-like shadow in the left upper lung field is noted. Attention is called to the wall thickness of this abscess or cavity compared to its total size; also to the comparative radiolucency of its central portion and the sharply demarcated peripheral border.

the nodular areas. The gross appearance of the cut surface following autopsy showed these areas to be round pneumonia-like areas of infiltration, many of which were lying close together. All four cases (figure 1) presented blotchy areas of increased density in the lung fields which resembled bronchopneumonic involvement.

Two cases presented definite discrete oval densities in the lung root shadows which were interpreted as and later demonstrated to be enlarged nodes in the lung root. All cases presented exaggerated hilar markings, far more than seen in the usual inflammations of pulmonary structures. The autopsies of the four cases re-

vealed enlarged hilar lymph nodes in each patient. The microscopic examination showed the nodes to be involved by coccidioidal granulomata.

One case, just prior to death, presented evidence of a beginning effusion between the right upper and middle lobes. At autopsy a right hydrothorax was present.

## Discussion

It is evident that a great many individuals who have been in the southwestern United States show a positive reaction to the coccidioidin skin test.

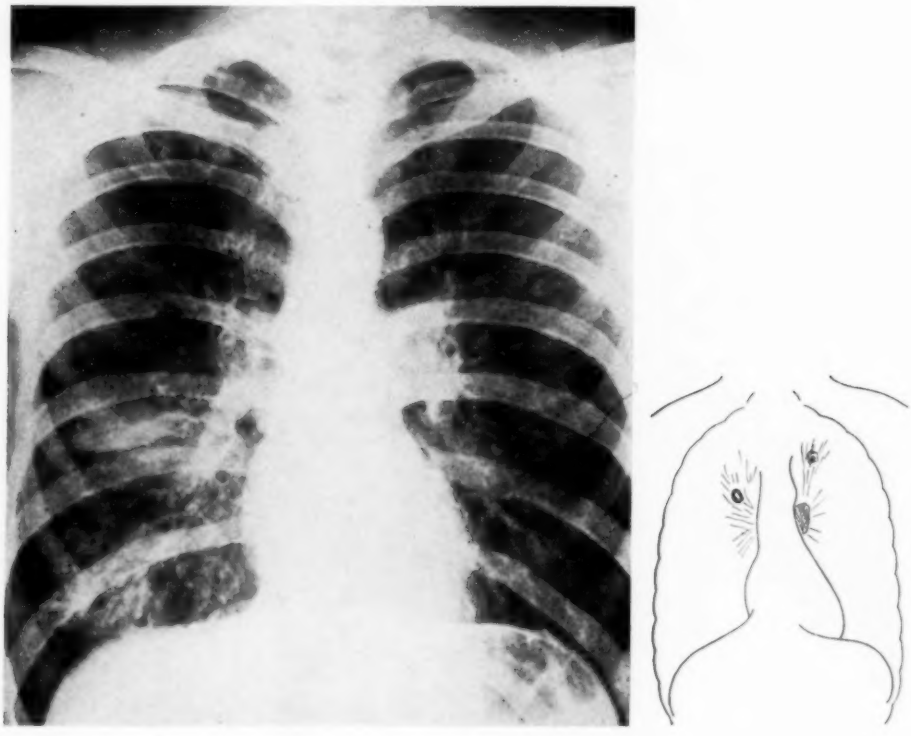

Fig. 7–A. The tendency for the thick walled annular shadow in the left upper lobe to assume a nodular type of lesion can be noted in this instance in a period of three months.

It is also apparent that of these individuals a sizeable percentage, the approximate number unknown, will exhibit roentgenographically persistent areas of increased density in the lungs of variable size and shape. These abnormal shadows probably will most often be considered to be tuberculous. If the lesion should prove to be tuberculous, it is likely to be potentially dangerous and would require supervision for a period of months or years in order to determine activity. If due to a coccidioidal infection, it is a relatively easy matter to determine the activity of the lesion which, if inactive, can be disregarded as a cause of future illness or disability. In certain in-

stances, much less numerous than with tuberculosis, other conditions will have to be distinguished from coccidioidomycosis.

The usual roentgenographic appearance of the initial focus or foci of pulmonary coccidioidomycosis is that of pneumonic infiltration. As the lesion changes, stabilizes, and heals, the residua in the lung fields assume such shapes as nodular, annular, linear, or a combination of all of these lesions. We have considered these lesions in individuals who have a positive coccidioidin skin test and negative tuberculin skin test to be due to coccidioidomycosis. If both skin tests are positive, it is not possible to tell with cer-

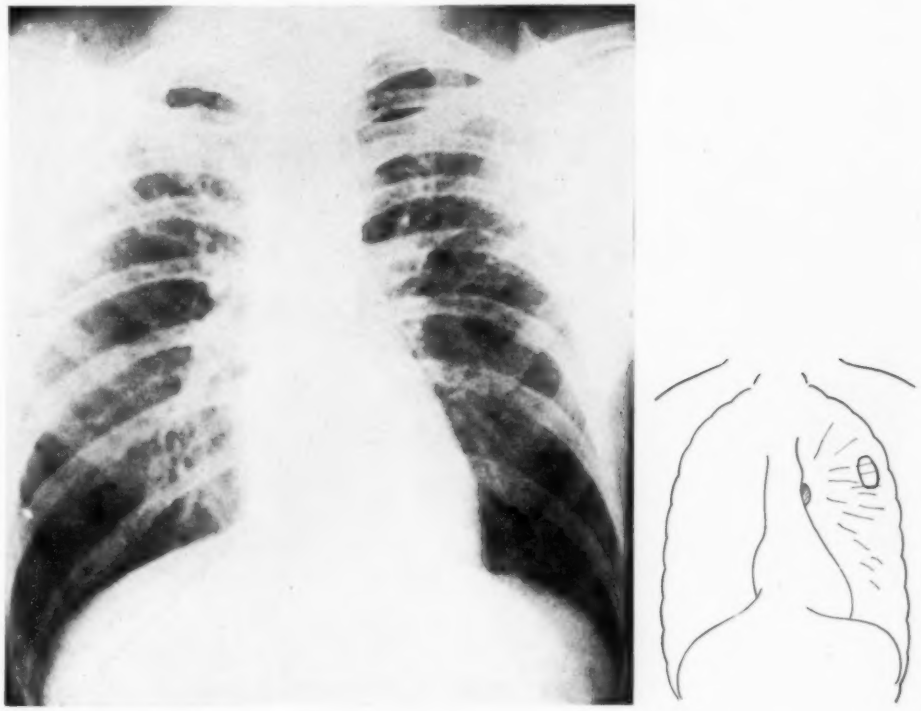

FIG. 8. The thin walled type of cavity (pneumatocoele) described by Winn and others has been conspicuous by its rarity in this group of cases as it has been observed only in two instances.

tainty the nature of the pulmonary lesions. However, some time during the course of the disease most cases of coccidioidomycosis show either definite or suggestive hilar adenopathy. The superinfection type (adult type) of tuberculosis is not associated with hilar adenopathy and although it is not possible to say definitely that a lung lesion associated with hilar adenopathy is due to coccidioidomycosis, the evidence favors such a diagnosis. The other pulmonary lesions that in our experience have occasionally to be differentiated from coccidioidomycosis are: (1) An old pneumonitis with residual scarring. Pneumonitis is frequently part of a bronchiectasis syn-

drome in which there may be nonspecific hilar adenopathy. (2) Boeck's sarcoid. It is seldom that the lesions of this condition, including involvement of the hilar lymph nodes, are limited to the lungs. Other criteria than lung lesions are needed to establish a diagnosis of sarcoid. (3) Metastatic malignant lesions of the lungs can usually be differentiated after a study.

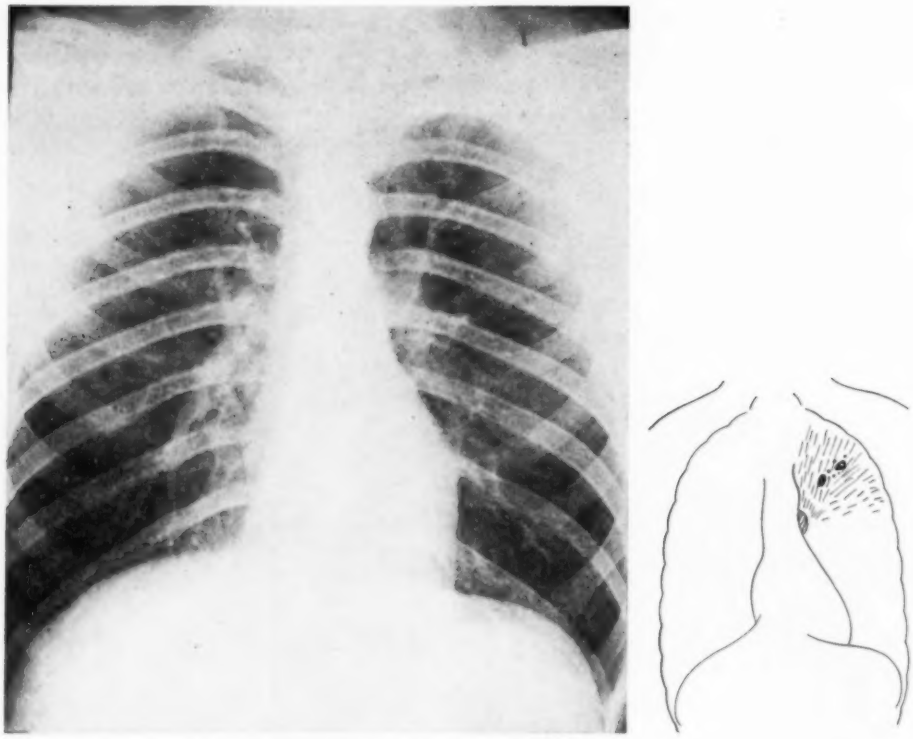

FIG. 9. Patient entered endemic area July 15, 1943. Onset of disease was apparently August 21, 1943, when he began having pain in left anterior mid chest which increased on inspiration with no cough. Physical examination was essentially negative. Skin test for coccidioidomycosis became positive on test November 18, 1943. Tuberculin test PPD No. 2 was negative, Kahn negative. Figure 9 shows an infiltrative process through the left apical region and sub-clavicular region which closely resembles that often seen in the adult type of tuberculosis. The possible identifying features which might make one suspect the presence of coccidioidomycosis are: first, an area which suggests a small thick-walled annular shadow intermingled with numerous round nodular shadows, and secondly the presence of the hilar adenopathy on the left.

This is particularly true of testicular tumor and hypernephroma in which the primary lesions can generally be demonstrated.

## SUMMARY

1. Three hundred and 72 patients who had spent time in the southwestern United States were tested intracutaneously for coccidioidomycosis. One hundred and 25 of these individuals gave a positive reaction to the skin test.

2. Of the positive reactors, 100 selected cases who showed a pulmonary lesion by roentgenogram during the period of observation were chosen for study. These individuals were also skin tested with tuberculin.

3. The lung lesions of 34 of the selected patients could be classified as coccidioidomycosis. Of the 34 patients nine showed *Coccidioides immitis* organisms in the sputum; 15 had a negative tuberculin skin test; and 10 showed *Coccidioides immitis* in the sputum by smear only, or lesions of coccidioidomycosis elsewhere than in the lungs.

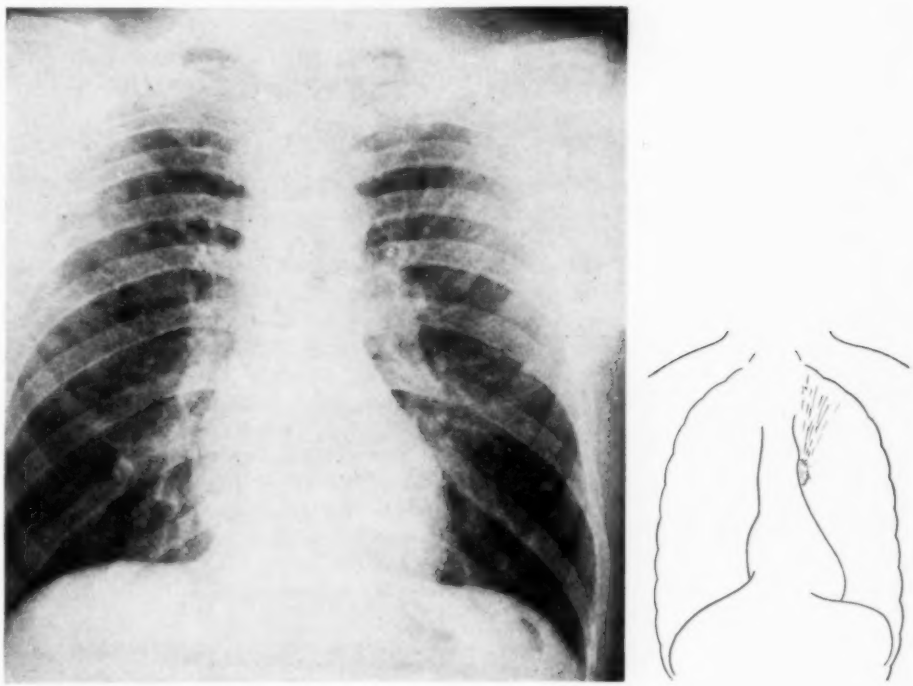

FIG. 9–A. Chest of same individual as in figure 9, approximately two months later with rapid resolution of the infiltrative process previously noted. This finding does not usually occur in tuberculosis. The hilar node persists.

The lung lesions in the remaining 66 patients who had a positive skin test for both coccidioidin and tuberculin were evaluated in the light of the experience with the known positive cases. Although a definite statement cannot be made, yet the evidence indicated that the lesions in 36 of these cases were due to coccidioidomycosis.

4. A pulmonary lesion by roentgenogram in an individual with a positive coccidioidin and tuberculin skin test was considered most likely to be coccidioidomycosis if the lesion was nodular, round, discrete, less than 3.5 cm. in diameter, of a density less than calcium but greater than the usual vascular

density in the hilum of the lung, and associated with suggestive or definite hilar adenopathy.

The authors wish to express their appreciation to Staff Sergeant William Roush and to Private Gaston Matifas for assistance in photographic and diagrammatic presentations.

## BIBLIOGRAPHY

1. Wernicke, R.: Ueber einen Protozoenbefund bei Mycosis fungoides (?), Centralbl. f. Bakt., 1892, xii, 859.
2. Posada, A.: Un nuovo caso de micosis fungoides con psorospermias, Ann. Circ. Med. Argentine, 1892, xv, 585.
3. Rixford, E., and Gilchrist, T. C.: Two cases of protozoan (coccidioidal) infection of the skin and other organs, Johns Hopkins Hosp. Rep., 1896, i, 209.
4. Ophuls, W.: Further observations on a pathogenic mould formerly described as a protozoan (*Coccidioides immitis, Coccidioides pyogenes*), Jr. Exper. Med., 1901, vi, 443.
5. Dickson, E. C., and Gifford, M. A.: Coccidioides infection (coccidioidomycosis), Arch. Int. Med., 1938, lxii, 853.
6. Smith, Charles Edward: Coccidioidomycosis, Med. Clin. N. Am., 1943, xxvii, 790–807.
7. Goldstein, David M., and McDonald, John B.: Primary pulmonary coccidioidomycosis, Jr. Am. Med. Assoc., 1944, cxxiv, 557–561.
8. Smith, David T.: Coccidioidal granuloma in Textbook of Medicine, Cecil, 6th Edition, W. B. Saunders Co., Philadelphia, 1943, 325–326.
9. Lee, Russell V., and Nixon, Norman: Syllabus on coccidioidomycosis. Headquarters, Army Air Forces Western Flying Training Command, Office of the Surgeon, Santa Ana, California, March 15, 1944.
10. Cronkite, A. E., and Loch, A. R.: Primary pulmonary coccidioidomycosis; experimental infection with *Coccidioides immitis,* Jr. Exper. Med., 1940, xxvii, 167–174.
11. Tager, M., and Liebow, A. A.: Intranasal and intraperitoneal infection of the mouse with *Coccidioides immitis,* Yale Jr. Biol. and Med., 1942, xv, 41–59.
12. Emmons, C. W., and Ashburn, L. L.: Isolation of *Haplosporangium parvum,* n. sp., and *Coccidioides immitis* from wild rodents; their relationship to coccidioidomycosis, Pub. Health Rep., 1942, lvii, 1715–1729.
13. Emmons, C. W.: Isolation of coccidioides from soil and rodents, Pub. Health Rep., 1942, lvii, 109.
14. Emmons, C. W.: Coccidioidomycosis in wild rodents. Method of determining extent of endemic areas, Pub. Health Rep., 1943, lviii, 1–5.
15. Dickson, Ernest C., and Gifford, Myrnie A.: Coccidioides infection (coccidioidomycosis). II. The primary type of infection, Arch. Int. Med., 1938, lxii, 853–871.
16. Smith, Charles E.: Epidemiology of acute coccidioidomycosis with erythema nodosum, Am. Jr. Pub. Health, 1940, xxx, 600–611.
17. McDonald, C.: *Coccidioides immitis,* Jr. Lab. and Clin. Med., 1934, xx, 47.
18. Loch, A. R.: Spherule formation and endosporulation of fungus coccidioides in vitro, Proc. Soc. Exper. Biol. and Med., 1938, xxxviii, 907–909.
19. Bump, W. S.: Growth of *Coccidioides immitis,* Jr. Infect. Dis., 1925, xxxvi, 561–565.
20. Jaffe, R. M.: Microscopic changes in coccidioidal granuloma, Virchow's Arch. f. path. Anat., 1930, cclxxviii, 42–61.
21. Carter, R. A.: Roentgen diagnosis of fungus infections of lungs, Radiology, 1943, xxxviii, 649–659.
22. Martin, C. L.: Roentgen ray findings in coccidioidosis, Texas State Jr. Med., 1942, xxxviii, 385–389.
23. Aronson, J. D., Saylor, R. M., and Parr, E. I.: Relationship of coccidioidomycosis to calcified pulmonary nodules (in Indian children with negative tuberculin reactions), Arch. Path., 1942, xxxiv, 31–48.

24. HIRSCH, E. F., and D'ANDREA, D.: Specific substance of *Coccidioides immitis,* Jr. Infect. Dis., 1927, xl, 633–637; Sensitization of guinea pigs with broth culture filtrate and with killed mycelium of *Coccidioides immitis,* Ibid., 638–640.

HIRSCH, E. F., and BENSON, H.: Specific skin and testes reaction with culture filtrate of *Coccidioides immitis,* Jr. Infect. Dis., 1927, xl, 629–633.

25. HURWITZ, S., YOUNG, J. E., and EDDIE, B. U.: *Coccidioides immitis* intradermal skin reactions; preliminary report of 449 cases, California and West. Med., 1938, xlviii, 87–89.

26. JACOBSON, H. P.: Coccidioidal granuloma, specific allergic cutaneous reaction; experimental and clinical investigations, Arch. Dermat. and Syph., 1928, xviii, 562.

27. KESSELL, J. F.: Coccidioidin skin test, Am. Jr. Trop. Med., 1939, xix, 199–204.

28. STEWART, R., and KIMURA, F.: Skin test for coccidioidal infection; preparation and standardization of coccidioidin, Jr. Infect. Dis., 1940, lxvi, 212–217.

29. WINN, W. A.: Coccidioidosis associated with pulmonary cavitation, Arch. Int. Med., 1941, lxviii, 1179–1214.

# SHORT P–R INTERVAL, PROLONGED QRS COMPLEX (WOLFF, PARKINSON, WHITE SYNDROME). REPORT OF FOURTEEN CASES AND A REVIEW OF THE LITERATURE *

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In 1930 Wolff, White and Parkinson [1] described a series of cases which showed an electrocardiographic picture of bundle branch block and a short P-R interval. This syndrome has since come to bear their names. It is characterized by attacks of paroxysmal tachycardia and carries only the danger attendant upon this phenomenon. The interim tracing shows a short P-R interval and prolonged QRS complex. It is considered essentially benign and these authors attribute these findings to vagal action. If this is removed by means of exercise or atropinization, the electrocardiogram is restored to normal.

Wolferth and Wood [2] and Holzmann and Scherf [3] independently suggested that an accessory pathway existed between the auricles and ventricles which short-circuited the impulse from the sinus node to the ventricular musculature without having it pass through the A-V node and bundle. This pathway corresponds to the one described by Kent [4] in 1914. Further evidence in support of this hypothesis was advanced by the experimental work of Butterworth and Poindexter [5] who, working with dogs, established an artificial electrical pathway between the auricles and ventricles. Stimulation of this demonstrated the electrocardiographic picture of the short P-R interval, and prolonged QRS complex. Reversal of the flow from ventricle to auricle caused typical auricular tachycardia. Histologic proof of the existence of accessory conduction connections between the auricles and ventricles was recently demonstrated by Wood, Wolferth and Geckeler [6] on a patient who before death presented this electrocardiographic picture.

This report includes 14 cases of the Wolff, Parkinson, White syndrome seen over a period of 18 months at an Army Regional Hospital. Some of these patients were asymptomatic, others presented complaints which were not suggestive of organic heart disease.

## Case Reports

*Case 1.* A 22 year old male who presented a history of attacks of tachycardia since 1940, six months prior to entry into the military service, had had about 20 attacks up until the time of first admission.

This soldier had been in the hospital on several occasions. The first time the electrocardiogram demonstrated a nodal paroxysmal tachycardia (rate 210 per min.) (figure 1*c*). Subsequent tracings taken during symptom-free periods showed biphasic

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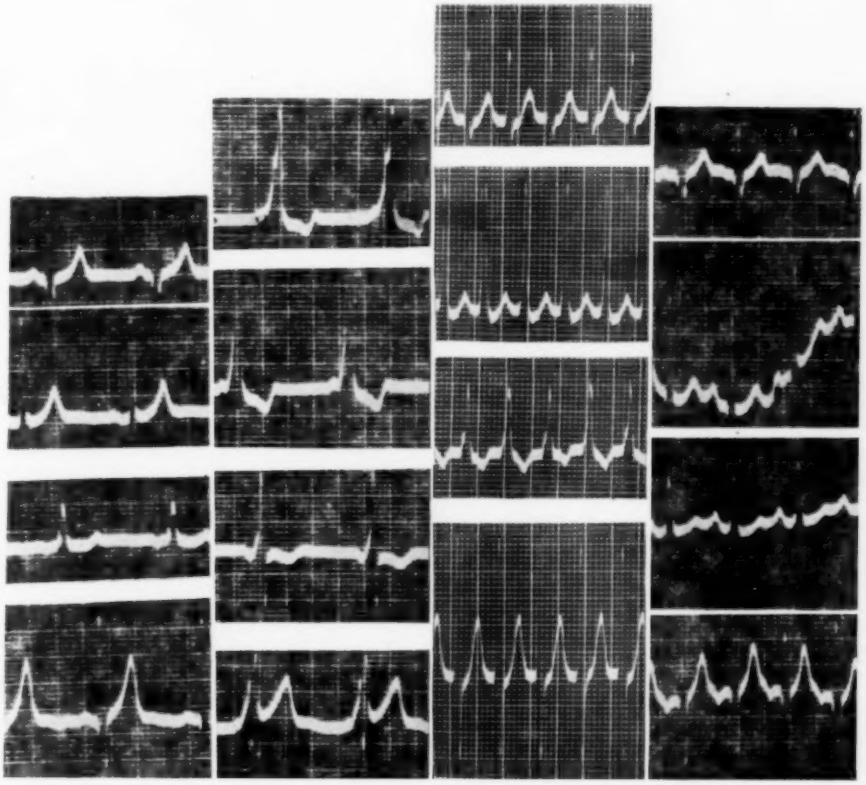
From ASF Regional Hospital, Fort Ord, California.

$T_{1, 2 \text{ and } 3}$, short P–R interval (.06 sec.) and prolonged QRS (.16 sec.) (figure 1*b*). The next electrocardiogram taken several months later was normal (figure 1*a*). Another taken two days later showed the short P–R interval (.06 sec.) and prolonged QRS (.16 sec.) only in the first lead. After moderate exercise these abnormalities disappeared (figure 1*d*). Administration of atropine, quinidine and digitalis in full doses at different intervals failed, however, to affect the path of the impulse.



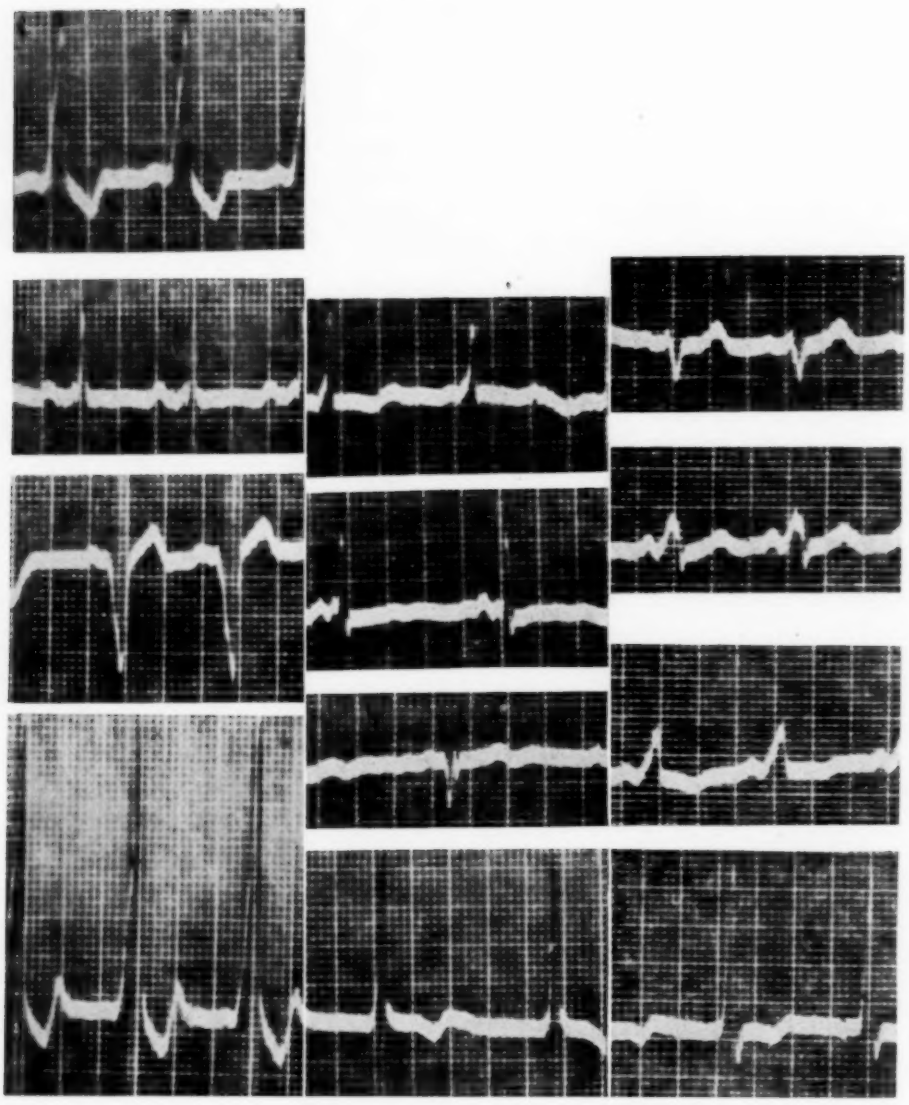
*a* *b* *c* *d*

FIG. 1. *Case 1.* (*a*) Normal tracing. (*b*) P–R interval .06 sec.; QRS complex .16 sec.; $T_{1, 2, 3}$ inverted. (*c*) Period of tachycardia. Nodal rhythm. (*d*) Findings disappeared following exercise.

In this case the pathway of the impulse shifted from the A–V bundle to the so-called bundle of Kent at different and unpredictable times. Increasing the cardiac rate by means of exercise was sufficient in this instance to restore the normal pathway.

*Case 2.* This 19 year old male complained of abdominal cramps and headaches of two years' duration. Examination: Blood pressure was 130 mm. Hg systolic and 90 mm. diastolic. No abnormal cardiac signs were found. Sedimentation rate was normal.

Electrocardiographic studies revealed a left axis deviation, P–R interval of .10 sec. and QRS complex of .16 sec., inverted $T_1$ and biphasic $T_4$ (figure 2*a*). No change was noted on further tracings taken after exercise, atropinization, or full courses of quinidine and digitalis.



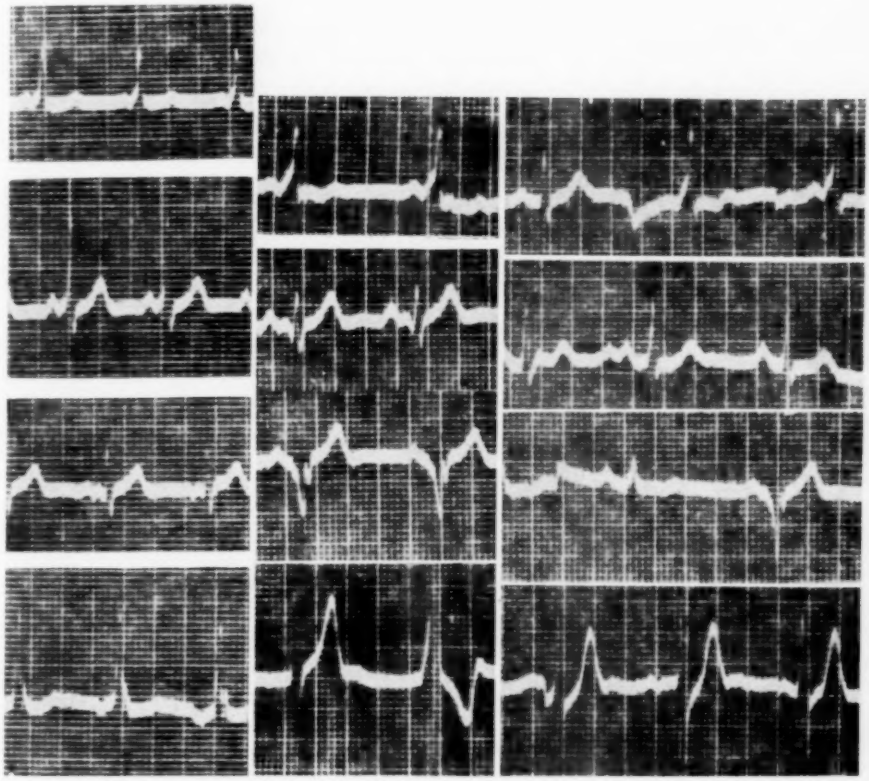
*a* *b* *c*

FIG. 2. *Case 2.* (*a*) P–R interval .10 sec.; QRS complex .16 sec.; $T_3$ inverted, $T_4$ biphasic. Left axis deviation. (*b*) *Case 3.* P–R interval .08 sec.; QRS complex .12 sec.; $T_1$ biphasic, $T_2$ low voltage, $T_4$ biphasic. Left axis deviation. (*c*) *Case 4.* P–R interval .08 sec.; QRS complex .16 sec. Left axis deviation (except in first lead where these values are normal), right axis deviation. $T_4$ biphasic.

*Case 3.* This 27 year old male presented no complaints whatever. Blood pressure was 120 mm. Hg systolic and 60 mm. diastolic. There were no unusual cardiac findings. Electrocardiogram showed a short P–R interval (.08 sec.), a prolongation of the QRS complex (.12 sec.), left axis deviation, biphasic $T_1$, low voltage $T_2$ and biphasic $T_4$ (figure 2*b*).

*Case 4.* Seven years before admission, following numerous family reverses, this 38 year old male had an attack of "rapid heart beat." Since that time he had been very "nervous." On admission he claimed to be short of breath on moderate exercise. Examination: Blood pressure was 140 mm. Hg systolic and 90 mm. diastolic. There were no abnormal cardiac findings.

Electrocardiographic studies demonstrated a P–R interval of .08 sec. and a QRS interval of .16 sec. (except in the first lead where these values were normal), right axis deviation and a biphasic $T_4$ (figure 2*c*). There was no appreciable change following a course of quinidine. Full digitalization produced a decrease in the QRS



*a* *b* *c*

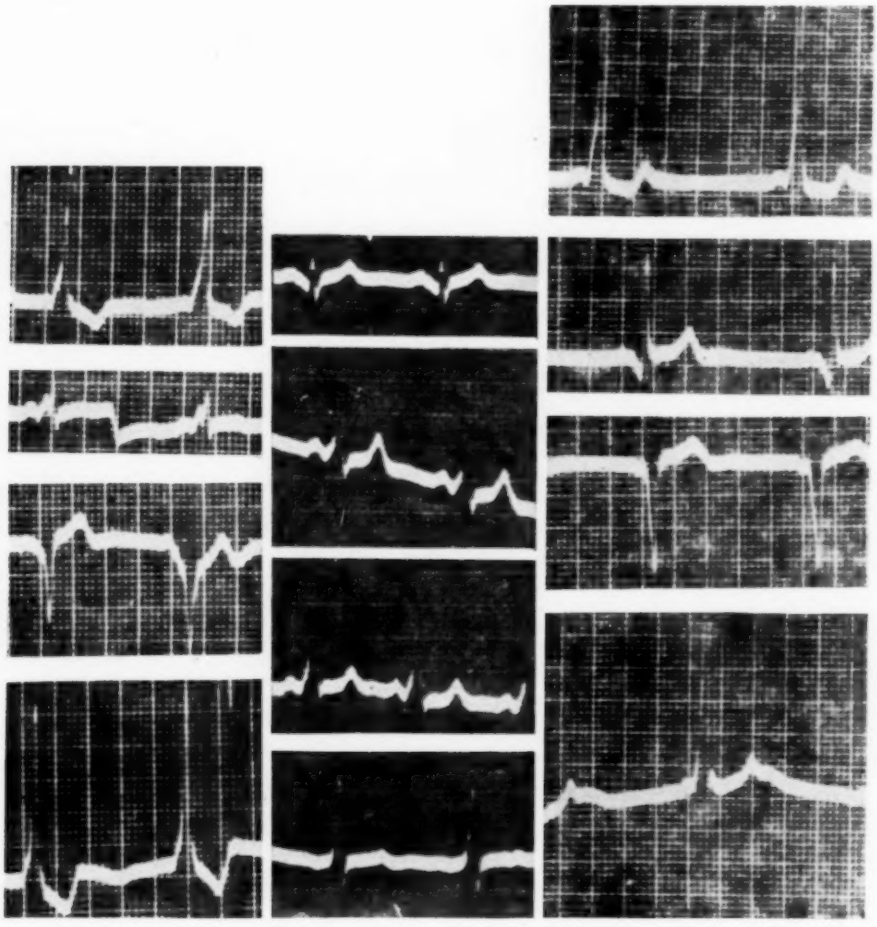
FIG. 3. (*a*) *Case 5.* P–R interval .08 sec.; QRS complex .12 sec. (*b*) *Case 6.* P–R interval .10 sec.; QRS complex .14 sec. Left axis deviation. Lead II is normal. In Lead IV three normal complexes are followed by a similar number of aberrant ones. (*c*) *Case 6.* Change of pathway of impulse (normal and aberrant) seen in Leads I and III.

interval in Lead I to .12 sec. and the expected depression and inversion of $RT_4$. The electrocardiogram was unaffected by exercise or the administration of full doses of atropine.

*Case 5.* On admission this 26 year old male had no complaints. Examination: Blood pressure was 140 mm. Hg systolic and 82 mm. diastolic. A short, soft systolic murmur was heard at the apex and pulmonic area. After exercise the latter murmur became harsh and was transmitted along the left border of the sternum. No thrills were felt.

Electrocardiographic investigation revealed a P–R interval of .08 sec. and a QRS of .12 sec. (figure 3*a*).

*Case 6.* This 24 year old male entered the hospital complaining of backaches and occasional sharp momentary left chest pain unrelated to exertion, over a period of years. No unusual cardiac signs were elicited. Routine laboratory studies were normal.



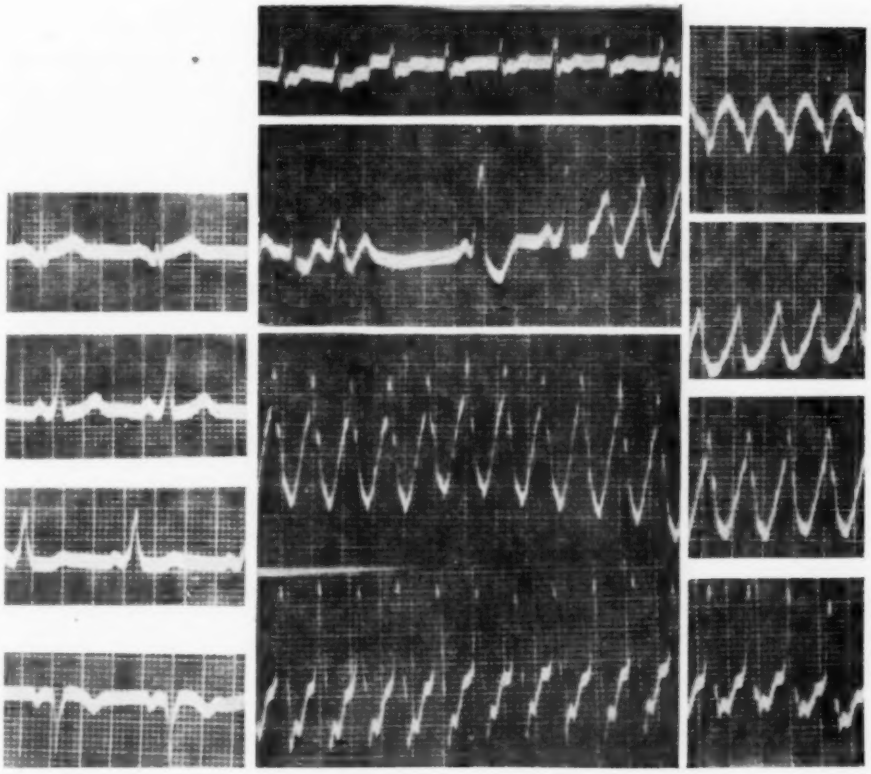
*a* *b* *c*

FIG. 4. (*a*) *Case 7.* P–R interval .08 sec.; QRS complex .12 sec.; $T_1$ inverted, $T_4$ biphasic. Left axis deviation. (*b*) *Case 8.* P–R interval .10 sec. and QRS complex .12 sec. in all but Lead I which is normal. These values are unaffected by exercise. (*c*) *Case 9.* P–R interval .08 sec.; QRS complex .13 sec.

The electrocardiogram showed a P–R interval of .10 sec. and QRS complex of .14 sec. and left axis deviation. The second lead was normal and in the fourth lead three normal complexes were followed by a similar number of aberrant ones (figure 3*b*). This patient showed a similar alternation in Leads I and III (figure 3*c*). At other times his tracings were practically normal. It is apparent that in this individual the path of the impulse from the sinus node was not a stable one.

*Case 7.* This 24 year old male complained of "smothering of his heart" at night which awakened him. This "smothering cut off his breath" and made him "hot and nervous." These symptoms have been present for two years before admission to the hospital. He denied ever having had rheumatic fever or hypertension. Examination: Blood pressure was 140 mm. Hg systolic and 80 mm. diastolic. No unusual cardiac findings were discovered.

The electrocardiogram demonstrated a P–R interval of .08 sec., QRS complex of



*a* *b* *c*

FIG. 5. (*a*) *Case 11.* P–R interval .10 sec.; QRS complex .12 sec.; $T_4$ inverted. No change after exercise. Slight changes in $T_4$ following atropinization. (*b*) *Case 11.* During an attack of tachycardia. Note that in Lead II there is a change from nodal tachycardia to several interval complexes (short P–R and prolonged QRS) and then the appearance of ventricular paroxysmal tachycardia. (*c*) *Case 11.* Same attack as seen in *b*. Ventricular paroxysmal tachycardia.

.12 sec., left axis deviation, inverted $T_1$ and biphasic $T_4$ (figure 4*a*). This picture was unaffected by exercise, atropine, and full doses of quinidine or digitalis.

*Case 8.* This 26 year old soldier stated he had had trouble with his "heart" since the age of 14 years. At that time he was confined to bed with polyarthritis and since has been unable to do strenuous activity because of pain and "fluttering" of his heart. He has also complained, during this period, of irregular pain and stiffness in his knees, ankles, and hip joints. On examination no abnormal physical signs were elicited.

Electrocardiographic studies revealed a P–R interval of .10 sec. and QRS complex of .12 sec. in all but the first lead. These features were unaffected by exercise (figure 4*b*).

*Case 9.* A young soldier on routine electrocardiographic studies revealed a left axis deviation, P–R interval of .08 sec. and a QRS complex of .13 sec. (figure 4*c*). Unfortunately this patient did not return so that his history and physical findings were unknown.

*Case 10.* A young soldier on routine electrocardiographic studies showed a P–R interval of .09 sec., QRS complex of .14 sec., depressed $RT_{1 \text{ and } 4}$, elevated $ST_3$, biphasic $T_4$, and left axis deviation. No essential change appeared following exercise.

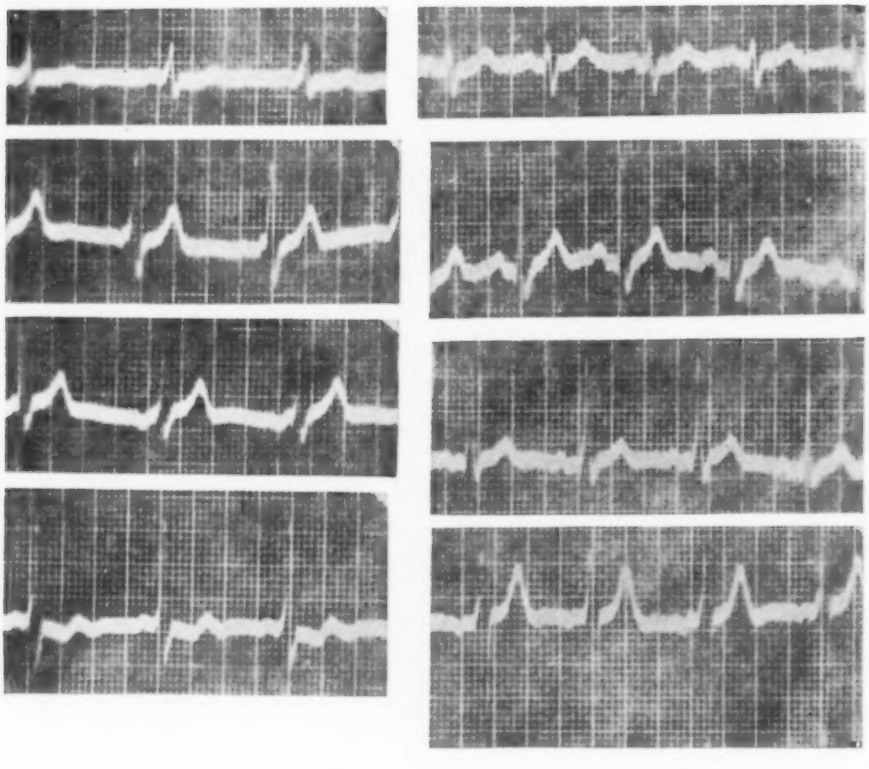


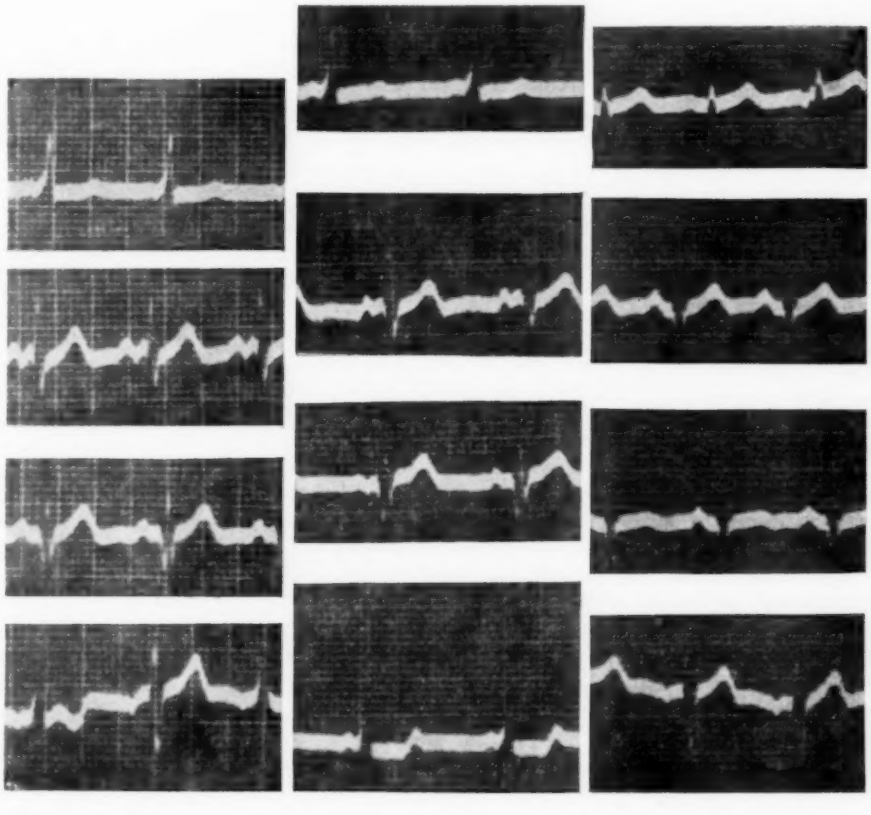
FIG. 6. *Case 12.* P–R interval .10 sec.; QRS complex .12 sec.; $T_4$ biphasic. Tracing taken two hours later, normal.

This soldier left the post immediately after this tracing was taken which prevented further clinical investigation.

*Case 11.* This patient was a 36 year old female who told of attacks of "rapid heart beat" since the age of 13 years. During these periods which endured for a few minutes to a few hours, she became dizzy and weak. She did not present any other complaints. She felt well enough between spells to engage in occupations requiring strenuous physical activity.

She was examined on numerous occasions and at no time were signs of organic heart disease found. Roentgenograms of her chest revealed the heart shadow within normal limits. Sedimentation rate determinations were normal. During one of her

attacks, she showed a picture of nodal tachycardia (figure 5*a, b, c*) which changed to a ventricular focus within a short space of time. Interim electrocardiographic studies showed a PR interval of .10 sec. and a QRS complex of .12 sec. and an inverted $T_4$. The administration of full doses of atropine produced only slight changes in $T_4$. Following the intake of quinidine sulfate gr. v four times daily over a period of three weeks, the fourth lead became normal. The course of the impulse, however,



*a* *b* *c*

FIG. 7. (*a*) *Case 13.* P–R interval .08 sec.; QRS complex .12 sec. Note that in Lead III these intervals are normal. In Lead IV abnormal and aberrant beats alternate. The rhythm is unaffected by exercise. (*b*) *Case 13.* No essential change following atropinization. (*c*) *Case 13.* Normal tracing following quinidine sulfate (20 grains daily over a three week period).

in the other three leads was unaffected, as manifested by the unchanged PR interval (.08 sec.) and QRS complex (.16 sec.), and $T_4$ was upright.

*Case 12.* This patient, a 25 year old male, presented a history of dizziness followed by "palpitation" when exercising or lifting heavy objects as well as while resting quietly in bed. The "palpitation" endured for 10 to 20 minutes and stopped suddenly with a "thump." Between attacks he felt well except for some moderate shortness of breath. Physical examination was essentially negative except for transient elevation of his blood pressure. Sedimentation rate was normal and no chamber enlargement was discovered during fluoroscopic examination of the heart.

The electrocardiographic picture consisted of a PR interval of .10 sec., QRS complex of .12 sec. and biphasic $T_4$. A tracing taken two hours later without any medication being given was normal in all respects (figure 6).

*Case 13.* This 18 year old soldier gave a history of having been struck by a car at six years of age. He was unconscious for two days. Since then he has had attacks of "rapid heart beat" on the average of about once a month, usually precipitated by sudden stooping or bending. Between attacks he felt perfectly well and demonstrated no symptoms of diminished cardiac reserve. During his stay in the hospital he contracted pneumonia from which he made an uneventful recovery. Examination of his heart did not reveal any abnormalities. Sedimentation rate and fluoroscopic studies were normal.

Electrocardiographic tracings revealed PR of .08 second and QRS of .12 second (figure *7a, b, c*). These findings were absent in the third lead and in the fourth lead normal and aberrant beats alternated. This rhythm was unaffected by exercise or atropinization. Quinidine therapy, 20 grains daily for three weeks, produced a normal configuration of the electrocardiogram. When this medication was discontinued the abnormal pathway again became ascendant. Subsequent administration of quinidine reversed this to normal. Digitalization had no appreciable effect on this patient's electrocardiogram.

This individual did not present a stable picture. Adequate doses of quinidine brought a reversal to the normal electrocardiographic pattern.

*Case 14.* A 26 year old soldier gave a history of attacks of "rapid heart beat" for five years before admission in June 1945, appearing and disappearing suddenly and lasting anywhere from five minutes to five hours. These attacks bore no relation to exertion and patient felt that there was no one cause for these disturbances. He did notice, at times, that he had a lot of "gas" in his stomach and he belched a great deal when in the midst of an attack. During the tachycardia he became extremely "nervous." In between attacks he felt perfectly well although he occasionally noticed a "skip" in his heart. He did not have any symptoms of diminished cardiac reserve and there was no history of rheumatic fever, diphtheria, or hypertension.

When seen for the first time patient had a cardiac rate of between 180 and 200 beats per minute. Moderate pressure on the left carotid sinus promptly restored a slow regular rate of about 84 per minute. No electrocardiogram was taken at that time. There were no other unusual findings on physical examination. Blood pressure was 110 mm. Hg systolic and 70 mm. diastolic.

Electrocardiogram taken on the day after admission revealed a short PR and prolonged QRS interval. There was no essential change in the configuration of this tracing after exercise, full atropinization, adequate doses of quinidine, and digitalization.

A search for foci of infection in dental, urological, ear, nose, and throat systems proved futile. Roentgenograms of the chest and gastrointestinal tract were normal. Gastric analysis showed an achlorhydria (7 per cent alcohol). However, following histamine administration, free hydrochloric acid was within normal limits. Kahn reaction, blood count and urinalysis were all normal.

## Discussion

Sufficient clinical and experimental data are now available for a rational explanation as to the course taken by the impulse in the heart of a patient with the Wolff, Parkinson, White syndrome. This pathway is not always the one of choice. In some individuals the sequence of events is a stable one; in others the aberrant bundle of Kent is employed irregularly. We can

see this in cases 1 and 6. On the other hand, in cases 2, 4 and 7 the short P-R interval and prolonged QRS complex appeared in the electrocardiogram consistently. In their original paper, Wolff, Parkinson, and White attributed the condition mainly to vagal influence, inasmuch as the release of vagal tone by exercise or atropinization produced a normal picture.

In Claggett's case [7] increasing the cardiac rate by means of exercise and atropine failed to produce a single normal complex.

*Effect of Atropine.* In this relation valuable information has been obtained through the use of various drugs. Diminishing the influence of the vagus by means of the administration of atropine should theoretically cause a return to normal rhythm. Claggett [7] was unsuccessful in his case in changing the electrocardiogram by atropine. We have produced the same effect (increasing the heart rate) through exercise, as noted in case 1, with resultant disappearance of the bundle-branch type of picture. On the other hand, we met with no success in the use of exercise or atropine in cases 2, 4, 7, 8, 11 and 13.

*Effect of Digitalis.* The effect of digitalis on this conduction disturbance has been tested. Theoretically, this drug should cause or perpetuate this picture. By depressing the A-V node, there would be encouragement for the use of the aberrant pathway.

Fox and Bobb [8] administered digitalis intravenously while the aberrant tissue was depressed and the conduction pattern normal, with resultant reappearance of the abnormal complex.

Similar findings were not obtained in our patients. Adequate digitalization did not affect the rhythm or conduction system in any of the patients who received this medication.

*Effect of Quinidine.* Because quinidine is considered to have greater affinity for the bundle of Kent, it is supposed to prevent this pathway from functioning in patients with a short P–R interval and a prolonged QRS complex. This would allow a normal course for the impulse through the A–V node and bundle, thus reëstablishing the normal electrocardiographic pattern.

This was so in Fox and Bobb's case.[8] However, in the instances in which we employed this measure, we met with success in only one or possibly two cases. One patient (case 13) received quinidine sulfate in daily doses of 20 grains. After a period of three weeks his rhythm returned to normal. Cessation of the drug brought a reappearance of the abnormal conduction path. A subsequent trial of quinidine repeated the initial results. However, cases 1, 2, 4 and 7 continued with the abnormal pattern despite full doses of quinidine.

*Clinical Picture.* Aside from attacks of ectopic tachycardias these patients do not present any symptoms.[9] It is not felt that the complaints in case 2 (abdominal cramps and headaches), case 4 (nervousness and shortness of breath), case 6 (backaches and chest pain), case 7 ("smothering" spells and nervousness), and case 8 (joint pains) have any relationship

to the unusual electrocardiographic pattern. Fluttering of the heart in case 8 may have been due to attacks of an ectopic rhythm. All too often the condition is discovered as an incidental finding during a routine electrocardiographic examination.

*Prognosis.* The outlook in these individuals is in general encouraging. Their life expectancy is unaffected and their usefulness as citizens is unimpaired. They are prone only to the dangers attendant to paroxysmal tachycardia or circus rhythms. Should these be allowed to proceed unchecked for considerable lengths of time, the possibility of decompensation ensuing is present. Wood, Wolferth and Geckeler's [6] patient succumbed in what was probably an attack of an ectopic tachycardia.

*Treatment.* The only indications for treatment are for the periods of tachycardia. The therapy herein involved is too well known and does not fall within the scope of this paper.

## Summary

1. Fourteen cases of Wolff, Parkinson, White syndrome are presented and a discussion of the literature undertaken.

2. The electrocardiographic findings are explained on the presence of an aberrant pathway between auricles and ventricles.

3. The expected results of the administration of such drugs as atropine and digitalis as described by some authors were not obtained with our patients. Quinidine sulfate depressed the abnormal pathway in only one, possibly two, of our cases. The remaining cases were unaffected.

Summary of Cases

| Cases | Stable | Exercise | Atropine | Digitalis | Quinidine |
|---|---|---|---|---|---|
| 1 | No | + | — | — | — |
| 2 | Yes | — | — | — | — |
| 3 | Yes (?) | | | | |
| 4 | Yes | — | — | — | — |
| 5 | Yes (?) | | | | |
| 6 | No | | | | |
| 7 | Yes | — | — | — | — |
| 8 | No (?) | — | | | |
| 9 | Yes (?) | | | | |
| 10 | Yes (?) | | | | |
| 11 | Yes (?) | — | — | — | + (?) in 4th lead |
| 12 | No | | | | |
| 13 | No | — | — | — | + |
| 14 | Yes | — | — | — | — |

+ Effective in restoring normal rhythm.
— No effect on ECG.

## BIBLIOGRAPHY

1. Wolff, L., White, P. D., and Parkinson, J.: Bundle branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia, Am. Heart Jr., 1930, v, 685.

2. Wolferth, C. C., and Wood, F. C.: The mechanism of production of short P–R intervals and prolonged QRS complexes in patients with presumably undamaged hearts: hypothesis of an accessory pathway of A–V conduction (Bundle of Kent), Am. Heart Jr., 1933, viii, 297.
3. Holzmann, M., and Scherf, D.: Ueber Elektrokardiogramme mit verkürzte Vorhof-Kammer-Distanz und positiven P-Zacken, Ztschr. f. klin. Med., 1932, cxxi, 404.
4. Kent, A. F. S.: Some problems in cardiac physiology, Brit. Med. Jr., 1914, ii, 105.
5. Butterworth, J. S., and Poindexter, C. A.: Short P–R interval associated with a prolonged QRS complex: a clinical and experimental study, Arch. Int. Med., 1942, lxix, 437.
6. Wood, F. C., Wolferth, C. C. and Geckeler, G. D.: Histologic demonstration of accessory muscular connections between auricle and ventricle in a case of short P–R interval and prolonged QRS complex, Am. Heart Jr., 1943, xxv, 454.
7. Claggett, H., Jr.: Short P–R interval with prolonged QRS complex: allergic manifestations and unusual electrocardiographic abnormalities, Am. Heart Jr., 1943, xxvi, 55.
8. Fox, T. T., and Bobb, A. L.: On the mechanism of the electrocardiographic syndrome of short P–R interval with prolonged QRS complex, Am. Heart Jr., 1944, xxviii, 311.
9. Bishop, L. F.: Bundle branch block with short P–R interval in individuals without organic heart disease, Am. Jr. Med. Sci., 1937, cxciv, 794.

# LIVER FUNCTION STUDIES IN DIABETES MELLITUS *

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The liver is intimately associated with the storage of glycogen, the maintenance of the normal blood sugar level and the formation of ketone bodies. The important rôle of the liver in carbohydrate metabolism makes the investigation of liver function in diabetes mellitus pertinent. The present communication is concerned with the study of hepatic disease as determined by the serum colloidal gold reaction in 247 patients with diabetes mellitus.

Although hepatic enlargement has been noted in patients with diabetes mellitus by White,[1] Hanssen,[2] Joslin,[3] Warren,[4] and Marble,[5] there are few conclusive reports in the literature of liver function studies in this disease. Rabinowitch [6] reported positive van den Bergh reactions in 34 of 130 patients with diabetes. He noted abnormal urobilinogen excretion in the urine in only three of 50 patients. Diamond,[7] however, found normal van den Bergh reactions in 14 of 17 diabetic patients. Meyer [8] observed hepatic dysfunction as determined by the quantitative van den Bergh reaction and urobilinogen excretion studies in 28 of 100 patients with diabetes mellitus. Hanssen [2] found a normal icteric index and urobilinogen excretion in diabetic patients with hepatic enlargement. Marble [5] also reported normal plasma bilirubin determinations in eight patients and normal cholesterol/cholesterol-ester ratios in 29 of 30 patients with diabetes mellitus.

## Methods

The serum colloidal gold reaction was selected for this study because of its marked sensitivity in detecting early liver disease. The reaction was found positive by one of us [9] in 92 per cent of patients with hepatic disease, false positive reactions occurring rarely in the control groups. The sensitivity and reliability of the colloidal gold reaction has been confirmed by Loew and Noth [10] and by Mateer and co-workers.[11] Sweet, Gray and Allen [12] found the test most sensitive in detecting liver disease in hepatolenticular degeneration, and Batty and Gray [13] utilized the reaction in investigating liver involvement in gall-bladder disease. Andersch [14] found the colloidal gold reaction exceedingly sensitive in evaluating the hepatic damage associated with sulfonamide therapy, and Maclagen [15] found "the test a valuable indicator of liver damage." Lavin, Sellek and del Frade [16] concluded from their studies that the serum colloidal gold test was "one of the most sensitive liver function tests." Similar results were obtained by Gidekel [17] and

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Forns [18] who reported the reaction to have "great sensitivity as an index of liver disease" and who recommended its routine use in the diagnosis of hepatic disease.

The serum colloidal gold reaction is based upon the fact that colloidal gold is precipitated by the diluted serum from a patient with hepatic disease but not by normal serum.[9] The mechanism of the reaction depends upon an increase in the gamma globulin and a decrease in the albumin content of the serum of patients with liver disease.[19] Five c.c. of acidified colloidal gold are added to 1 c.c. of serum diluted to 1:3,500, 1:7,000, and 1:14,000 as described in previous reports.[13] The degree of flocculation is recorded as in the Lange reaction. A positive reaction is represented by complete flocculation in one or more dilutions.

The 247 patients with diabetes were divided into two groups. Group A consisted of 99 patients who had been under careful supervision for the management of their diabetes in a private institution for several years. Their diet, insulin requirement and general care were subject to fairly careful control. Group B was composed of 148 patients receiving treatment for diabetes in a charity institution. The economic, social and intellectual status of this group made dietary control and insulin treatment more difficult. Clinic visits were less frequent in Group B than in Group A, and the general care of these patients regarding infections, vitamin intake and control of the blood sugar levels was not equal to that of Group A.

The incidence of liver disease in the obese and non-obese patients was studied in both groups. An increase in weight of more than 10 per cent over the standard weight was considered evidence of obesity. Observations in the age groups of patients under 35 and over 35 years of age were also made.

The frequency of positive liver tests in mild and severe diabetes was investigated. The 247 patients were divided arbitrarily into two groups. Those requiring less than 25 units of insulin daily were placed in the classification of mild diabetes, and the others requiring 25 or more units of insulin daily were defined as severe diabetics.

The relationship of liver involvement to the proper control of the diabetes was investigated. The factors noted in evaluating the control of the diabetes were the level of hyperglycemia, glycosuria, acidosis, hypoglycemia, infections and other complications, insulin resistance and rapid fluctuations in insulin requirement. The incidence of positive liver tests in patients with acidosis or coma was studied also.

## Results

The serum colloidal gold reaction was positive in 91 of the 247 patients with diabetes, an incidence of 36.8 per cent (table 1). Positive reactions occurred more frequently in the 148 patients of Group B (43.2 per cent) than in the 99 patients of Group A (27.1 per cent).

TABLE I

Incidence of Liver Disease in Diabetes

| | Number of Patients | Positive Serum Colloidal Gold Reactions |
|---|---|---|
| Group A | 99 | 27 (27.1%) |
| Group B | 148 | 64 (43.2%) |
| Total | 247 | 91 (36.8%) |

The test was positive in 28 of the 66 obese patients (42.4 per cent) as compared with 63 of the 181 patients (34.8 per cent) in the non-obese group (table 2). In Group B the incidence appeared to be higher in both the obese (59.2 per cent) and non-obese patients (39.6 per cent) than in the corresponding patients of Group A in which positive results were observed in 30 per cent and 25 per cent respectively.

TABLE II

Incidence of Liver Disease in Obese and Non-Obese Diabetic Patients

| | Obese Patients | Positive Liver Tests | Non-Obese Patients | Positive Liver Tests |
|---|---|---|---|---|
| Group A | 39 | 12 (30%) | 60 | 15 (25%) |
| Group B | 27 | 16 (59.2%) | 121 | 48 (39.6%) |
| Total | 66 | 28 (42.4%) | 181 | 63 (34.8%) |

There appeared very little difference between the incidence of liver involvement in patients under 35 years of age (43.4 per cent) and that in the older age group (34.8 per cent). Here again the percentage was higher in Group B (48.4 per cent and 41.7 per cent) than in Group A (30.7 per cent and 25.5 per cent) (table 3).

Hepatic disease appeared to be much more prevalent in severe diabetes than in mild diabetes. The colloidal gold reaction was positive in 62 of 123

TABLE III

The Relation of Age to Positive Liver Tests in Diabetic Patients

| | Number of Patients | Positive Serum Colloidal Gold Reactions |
|---|---|---|
| *Under 35* | | |
| Group A | 13 | 4 (30.7%) |
| Group B | 33 | 16 (48.4%) |
| Total | 46 | 20 (43.4%) |
| *Over 35* | | |
| Group A | 86 | 22 (25.5%) |
| Group B | 115 | 48 (41.7%) |
| Total | 201 | 70 (34.8%) |

patients with severe diabetes (49.9 per cent) compared with 29 of 124 patients with mild diabetes (23.3 per cent) (table 4). Positive tests were observed with almost equal frequency among the patients of Group A and Group B, with severe diabetes, occurring in 47.2 per cent of the former and 52.3 per cent of the latter. Among the mildly diabetic patients, however, the incidence was higher in Group B (30.6 per cent) than in Group A (16.1 per cent).

TABLE IV

Incidence of Positive Liver Tests in Mild and Severe Diabetes

| | Number of Patients | Incidence of Positive Colloidal Gold Reaction |
|---|---|---|
| *Mild Diabetes* | | |
| Group A | 62 | 10 (16.1%) |
| Group B | 62 | 19 (30.6%) |
| Total | 124 | 29 (23.3%) |
| *Severe Diabetes* | | |
| Group A | 37 | 17 (47.2%) |
| Group B | 86 | 45 (52.3%) |
| Total | 123 | 62 (49.9%) |

The highest incidence of liver involvement occurred in the poorly controlled diabetic patients (table 5). The colloidal gold test was positive in 48 of 84 patients (57.1 per cent) with essentially the same incidence in Group A (54 per cent) and Group B (58.6 per cent). This is to be contrasted with the occurrence of hepatic disease in only 43 of 163 patients

TABLE V

Positive Liver Tests in Well Controlled and Poorly Controlled Diabetes

| | Number of Patients | Incidence of Positive Colloidal Gold Reaction |
|---|---|---|
| *Well Controlled* | | |
| Group A | 73 | 13 (17.7%) |
| Group B | 90 | 30 (33.3%) |
| Total | 163 | 43 (26.3%) |
| *Poorly Controlled* | | |
| Group A | 26 | 14 (54%) |
| Group B | 58 | 34 (58.6%) |
| Total | 84 | 48 (57.1%) |

(26.3 per cent) with well controlled diabetes (table 5). Among these patients positive tests were more prevalent in Group B (33.3 per cent) than in Group A (17.7 per cent).

Twenty-two patients were in diabetic coma or acidosis when their liver function was studied. In 17 of these, or 77.2 per cent, positive colloidal gold reactions were observed (table 6).

TABLE VI

Incidence of Hepatic Disease in Diabetic Acidosis and Coma

| Number of Patients | Positive Serum Colloidal Gold Reactions |
|---|---|
| 22 | 17 (77.2%) |

## DISCUSSION

It has been known for a long time that the diabetic patient is susceptible to fatty infiltration of the liver [1, 2] and to depletion of the liver glycogen.[3, 4] It was not surprising, therefore, to find evidence of liver involvement in 36.8 per cent of the 247 diabetic patients studied. This incidence of hepatic disease was somewhat higher than that reported by Meyer [5] and Rabinowitch.[6]

Newburgh and his associates have described a syndrome of hyperglycemia, glycosuria and a decreased glucose tolerance occurring in obese individuals and resulting presumably from fatty infiltration of the liver.[20] A higher incidence of liver involvement in obese than in non-obese patients could be anticipated from his studies. However, there was no significant statistical difference in the incidence of positive colloidal gold reactions in the 66 obese and 181 non-obese diabetic patients reported in this section (table 2). This may be explained by Newburgh's observation that the "glucose tolerance is unimpaired until the obesity has existed for more than 11 years."[20a] Since many of the patients reported in table 2 had not been obese for more than five or six years, not enough time had elapsed, apparently, to produce a fatty infiltration of the liver.

Although diabetes is usually more severe in the young than in the aged, there was no significant statistical difference in the incidence of hepatic involvement in the two groups (table 3). The greater regenerative powers of the liver in the young[4] and the shorter duration of the disease may have compensated for the increased severity of the diabetes.

There was a most striking difference in the incidence of positive colloidal gold reactions in the 124 patients with mild diabetes when compared with the 123 patients with severe diabetes. The liver test was positive in 23.3 per cent of the mild diabetics and in 49.9 per cent of the severe diabetics, an increase of over 100 per cent (table 4).

The high incidence of positive liver tests in severe diabetes is presumably the result of fatty infiltration of the liver which is a common occurrence in this disease. The extreme degree of fatty infiltration of the liver occurring in depancreatized dogs is well known,[21] and it is probable that the hepatomegaly commonly observed in juvenile and adult diabetics represents fatty infiltration of the liver in most instances.

Failure to control the diabetic state properly results in a considerable increase in the incidence of liver disease. The effects of poor diabetic control on the liver have been observed by White[1] who reported the common occurrence of fatty infiltration of the liver in poorly treated diabetic children. The liver decreased in size after the administration of insulin and the institution of diabetic management. Failure to control the diabetes in experimental animals, moreover, has resulted in marked fatty infiltration of the liver.[22]

The frequency of hepatic involvement in the 247 diabetic patients under discussion was increased from 26.3 per cent in the well controlled diabetics to 57.1 per cent in the poorly controlled group (table 5). This represents an increase of more than 100 per cent in the latter group and emphasizes the importance of the proper regulation of this disease.

In reviewing tables 1 to 3 it was observed that the patients in Group B consistently demonstrated a higher incidence of liver involvement than those in Group A. Positive tests were noted in 16.1 to 29.2 per cent more patients in Group B. The determining factors in this discrepancy between the two

groups were the lapses of insulin therapy and the lack of general care in regard to the diet and infections. Since the patients in this group were at a lower intellectual and economic level than those in Group A, differences in dietary habits and the intelligent use of insulin were important considerations. This was confirmed by the fact that in the poorly controlled diabetics (table 5) and in the severe diabetics (table 4) the incidence of positive liver tests was essentially the same in both groups.

An exceedingly high incidence of hepatic disease was observed in 22 patients with acidosis or coma. Positive colloidal gold reactions occurred in 17 instances, or 77.2 per cent (table 6). In liver disease there appears to be a disturbance in the functional capacity of the liver cells to deposit glycogen. This can be demonstrated by the use of hepatotoxic agents and has been observed in association with diseases of the liver.[23] When the liver reserves of glycogen are depleted, ketonemia is more likely to occur.[24] There is a definite relationship between hepatic disease, glycogen reserve and ketosis.[25] The importance of a high carbohydrate diet in this group is quite evident.

These studies of the colloidal gold reaction in diabetes support the views of Soskin [26] and others that there is a close relationship between hepatic disease and diabetes. It is generally recognized that the glycogen stores of the liver have an important bearing upon its functional capacity and upon its resistance to hepatotoxic agents. In diabetes the glycogen stores of the liver are frequently depleted and are replaced by fat, particularly in the severe manifestations of the disease. The high incidence of positive colloidal gold reactions in these cases emphasizes the importance of the liver disease in severe diabetes.

The liver, moreover, is the principal organ for the homeostatic regulation of the blood sugar level. Soskin and his associates have noted that whenever the blood sugar tends to rise above the normal level, the liver responds by diminishing its output of sugar into the blood. Insulin is an important factor in the endocrine balance which controls the level at which the liver regulates the blood sugar, but the intrinsic homeostatic regulating mechanism of the liver is thought to be the most important factor of all.[26]

When the liver is abnormal, the mechanism by which it regulates the blood sugar is greatly impaired, and its response to insulin is diminished. The detection of liver disease in approximately 50 per cent of patients with severe diabetes may be of considerable significance in the dietary and medical management of the disease.

## Summary

1. The serum colloidal gold reaction was positive in 91 of 247 patients with diabetes, an incidence of 36.8 per cent. Liver involvement was observed more frequently in the 148 patients receiving irregular care (43.2 per cent) than in the 99 patients under constant supervision (27.1 per cent).

2. The reaction was positive in 62 of 123 patients with severe diabetes (49.9 per cent) in contrast to 29 of 124 patients (23.3 per cent) with mild diabetes.

3. The frequency of hepatic involvement was increased from 26.3 per cent in the well controlled diabetics to 57.1 per cent in the poorly controlled group.

4. The highest incidence of hepatic disease was found in 22 patients with diabetic acidosis or coma. The test was positive in 17 instances (77.2 per cent) in this group.

5. Positive reactions were observed in 28 of 66 obese patients (42.4 per cent) as compared with 63 of the 181 non-obese patients (34.8 per cent).

6. The incidence of liver involvement was 43.4 per cent in the patients under 35 years of age and 34.8 per cent in the older age group.

## Conclusions

1. Diabetes mellitus is associated frequently with disease of the liver as is evidenced by the presence of a positive serum colloidal gold reaction.

2. Hepatic involvement is much more prevalent in severe than in mild diabetes.

3. Failure to control the diabetic state properly results in a considerable increase in liver disease as is seen particularly in patients with acidosis or coma.

4. There is no statistically significant difference between the frequency of liver involvement in the younger and older age groups and that in obese and non-obese patients.

## BIBLIOGRAPHY

1. White, P.: Diabetes in childhood and adolescence, 1932, Lea and Febiger, Philadelphia, p. 169.
2. Hanssen, P.: Enlargement of the liver in diabetes, Jr. Am. Med. Assoc., 1936, cvi, 914.
3. Joslin, E. D.: The treatment of diabetes mellitus, 1937, Lea and Febiger, Philadelphia, p. 102.
4. Warren, S.: The pathology of diabetes mellitus, 1938, Lea and Febiger, Philadelphia, p. 82.
5. Marble, A., White, P., Bogan, I. K., and Smith, R. M.: Enlargement of the liver in diabetic children, Arch. Int. Med., 1938, lxii, 740.
6. Rabinowitch, J. M.: Note on the bilirubin content of blood and urobilinogen content of urine in diabetes mellitus, Brit. Jr. Exper. Path., 1936, xvii, 249.
7. Diamond, J. S.: The value of routine estimations of blood bilirubin, Am. Jr. Med. Sci., 1928, clxxvi, 321.
8. Meyer, E. L.: Hepatic function in diabetes, Arch. Int. Med., 1931, xlvii, 182.
9. Gray, S. J.: The colloidal gold reaction of blood serum in diseases of the liver, Arch. Int. Med., 1940, lxv, 524.
10. Loew, E. R., and Noth, P.: Hepatic dysfunction in relation to the reaction of blood serum and colloidal gold, Am. Jr. Physiol., 1941, cxxxiii, 364.
11. Mateer, J. G., Baltz, J. I., Marion, D. F., Hollands, R. A., and Yagle, E. M.: A comparative evaluation of the newer liver function tests, Am. Jr. Digest. Dis., 1942, ix, 13.

12. Sweet, W. H., Gray, S. J., and Allen, J. G.: Clinical detection of hepatic disease in hepatolenticular degeneration, Jr. Am. Med. Assoc., 1941, cxvii, 1613.
13. Batty, J. L., and Gray, S. J.: Involvement of the liver in disease of the gall-bladder, Arch. Int. Med., 1943, lxxii, 176.
14. Andersch, M. A.: Changes in liver function test during sulfonamide therapy, Ann. Int. Med., 1943, xix, 622.
15. Maclagen, N. F.: The serum colloidal gold reaction as a liver function test, Brit. Jr. Exper. Path., 1944, xxv, 15.
16. Lavin, R., Sellek, A., and del Frade, A.: Sobre la reaccion del oro coloidal de Lange en el suero sanguineo para el diagnostico de las hepatopatias, Vida nueva, 1942, xvi, 203.
17. Gidekel, S.: Tecnica de la reaccion del oro coloidal en el suero para utilizala segun Gray, Rev. med. de Rosario, 1944, xxxiv, 47.
18. Forns, J. S.: Volor clinico de las pruebas functionales hepaticis basadas en las alteraciones de las proteinas hematicis, Rev. clin. españ., 1943, ix, 173.
19. Gray, S. J., and Barron, E. S. G.: The electrophoretic analyses of the serum proteins in diseases of the liver, Jr. Clin. Invest., 1943, xxii, 191.
20. (a) Newburgh, L. H., and Conn, J. W.: A new interpretation of hyperglycemia in obese middle aged persons, Jr. Am. Med. Assoc., 1939, cxii, 7.
(b) Newburgh, L. H.: Control of the hyperglycemia of obese "diabetics" by weight reduction, Ann. Int. Med., 1942, xvii, 935.
21. Allen, F. N., Bowie, J. J., Macleod, J. R., and Robinson, W. L.: Behavior of depancreatized dogs kept alive with insulin, Brit. Jr. Exper. Path., 1924, v, 75.
22. Dragstedt, L. R., Vermeulen, C., Goodpasture, W. C., Donovan, P. B., and Geer, W. A.: Lipocaic and fatty infiltration of the liver in pancreatic diabetes, Arch. Int. Med., 1939, lxiv, 1017.
23. Conn, J. W., Newburgh, L. H., Johnson, M. W., and Sheldon, J. M.: A study of deranged carbohydrate metabolism in chronic infectious hepatitis, Arch. Int. Med., 1938, lxii, 765.
24. Mirsky, A., and Nelson, W. E.: Ketosis in relation to the hepatic reserves of glycogen, Am. Jr. Dis. Child., 1944, lxvii, 100.
25. Barach, J. H.: Ketosis in health and disease, Am. Jr. Digest. Dis., 1943, x, 134.
26. Soskin, S.: The blood sugar: its origin, regulation and utilization, Physiol. Rev., 1941, xxi, 140.

# WHAT CAN BE ACCOMPLISHED IN THE TREATMENT OF HEART DISEASES *

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It is not out of place now and then to take stock of what we can expect at the time as the maximum hope in the treatment of diseases of the heart. Especially is this an encouraging process when we bring into focus the tremendous advances that have been made in this field in the last quarter of a century. Diseases which were long thought to be beyond relief are now being treated by surgical and medical means with the appearance of cure.

*Congenital Heart Disease.* It is fitting that I should mention congenital heart disease first. Until recently nothing corrective could be done in the treatment of patients suffering from these defects. However, a new field was explored and opened when Gross [1, 2, 3] daringly conceived and executed the operation of ligation of a patent ductus arteriosus and apparently restored the circulation to a normal status. In this defect there is flow of blood from aorta to pulmonary artery by way of a patent ductus arteriosus. Ample cases have been subjected to this procedure to indicate that it can be carried out by competent surgeons with a minimum of mortality. When left to their natural course the outlook for these patients is usually one of heart failure or of bacterial endocarditis.[4] The operation appears indicated in those patients showing evidence of decreased circulation, namely underdevelopment and undernutrition [5] or evidence of subacute bacterial endocarditis.[6] Since this congenital defect is now subject to surgical cure, it is important that these cases be recognized and given the benefit of consideration for operation. The essential features contributing to the diagnosis are: continuous machinery murmur over the pulmonic area, pulmonary conus enlargement, thrill over the pulmonic area, wide pulse pressure, absence of axis deviation in electrocardiogram, left ventricular enlargement in roentgenogram, increased pulsation of the pulmonary artery, pulmonary vessels and left ventricular margin, absence of cyanosis, and stunted growth. It occurs in females twice as often as in males. Only those patients with uncomplicated patency of the ductus arteriosus should be subjected to operation. Only recently, Blalock and Taussig [7] have reported an operation for increasing the flow of blood through the lungs with the intention of reducing the cyanosis in patients with congenital malformations of the heart with pulmonary stenosis or atresia. The operation consists in making an anastomosis between a branch of the aorta and one of the pulmonary arteries. An artificial patent ductus arteriosus is created.

Although it is important and satisfying to arrive at a correct diagnosis,

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many of the congenital cardiac defects are multiple and present such complicated physical signs that accurate diagnosis is not always possible at present. One should recognize coarctation of the aorta in order to separate subjects exhibiting this from other patients with hypertension, both with respect to the natural history and complications, and also to spare such patients splanchnic resection for lowering the blood pressure. Moreover, the surgical approach to the rectification of the defect prevailing in coarctation of the aorta has been made recently by Gross and Hufnagel [3a] by resection of the zone of constriction with end to end anastomosis of the proximal and distal ends of the aorta. The presence of hypertension in the upper extremities, with lower or absent blood pressure and pulses in the femoral, popliteal, dorsalis pedis and posterior tibial vessels, enlargement of the heart to the left, a systolic murmur over the base of the heart, and scalloping of the lower margins of the ribs by erosion caused by the intercostal arteries, make up the clinical picture of coarctation of the aorta.[8, 9] It is urgent, therefore, in every patient exhibiting hypertension to measure the blood pressure in the legs as well as in the arms.

In my opinion insufficient information can be secured by diodrast visualization to warrant the dangers inherent in its injection.[10]

*Chronic Constrictive Pericarditis.* Chronic constrictive pericarditis or Pick's disease is another disease which can be cured in suitable cases by surgical intervention. Churchill, in Boston, first stimulated interest in pericardiectomy in this country.[11] He demonstrated that the operation could be safely carried out, and cured certain patients. Heuer, at the New York Hospital, has operated on 18 patients whom I have observed.[12, 13, 14] Beck,[15] Blalock [16] and Harrington [17] have also had a wide experience in this field. It is imperative that physicians recognize these cases and separate them from other cases of heart failure. In any patient who presents a picture of heart failure but in whom the usual common etiological causes are not found, that is, who show no evidence of rheumatic valvular disease, arteriosclerosis or hypertension, the diagnosis of chronic constrictive pericarditis should be considered.[13] There are venous engorgement, enlargement of the liver, ascites, edema, pleural effusion, small or not greatly enlarged heart, small pulse pressure, paradoxical pulse, small or absent pulsations of the heart under fluoroscopy and in roentgenkymograms, fixation of the heart in the chest on fluoroscopy and of the electrical axis of the electrocardiogram and low amplitude of the QRS complexes of the electrocardiogram. Calcification may be found on fluoroscopy and in the roentgenograms.[18] The signs and symptoms are due to the thickened pericardium obstructing the passage of blood through the heart: the heart is unable to relax in diastole to admit blood to its cavities, and is unable to contract completely in systole to expel blood from its cavities.[19] The venous pressure is elevated, the circulation time is prolonged, and the cardiac output per beat and per minute decreased. Dissecting off the parietal and visceral pericardium from as much of the anterior surface of the heart as possible, enabling it to herniate out through

this window, so improves the function of the heart that the circulation returns to normal limits and the patient improves and is restored to normal health and activity.[14]

We have followed patients from the stage of acute pericarditis with effusion through absorption of the fluid and then constriction by the thickening pericardium. Patients are leading normal lives after operation, as compared with invalidism beforehand. Improvement may be rapid, a matter of weeks, or it may take months or upward of a year for maximum benefit to be accomplished.[14] The care of these patients illustrates the benefits which accrue from the close collaboration of physician and surgeon.

*Carotid Sinus Syndrome.* This syndrome is characterized by hypersensitivity of one or both of the carotid sinuses. The bulbous enlargement at the bifurcation of the carotid artery into its external and internal branches is supplied with a plexus of nerve fibers through which impulses are mediated which aid in the maintenance of blood pressure. Pressure on the carotid sinus induces slowing of the heart and moderate fall in blood pressure. In marked hypersensitivity of the carotid sinuses, pressure on the sinus results in marked cardiac slowing even to asystole, fall in blood pressure to zero, and syncope.[20] Lesser grades of sensitivity result in slowing of heart rate, fall in blood pressure and dizziness. One or both sinuses may be hypersensitive. This *vagus* type is the most common. This type of reaction is abolished by atropine and by novocainization of the sinus. There is also a *depressor* type in which syncope results from cerebral anoxia due to fall in systemic blood pressure and a *cerebral* type in which syncope occurs without change in heart rate or blood pressure.[20] In those patients with hypersensitivity of the carotid sinus, attacks of syncope may be precipitated by turning the head, wearing a tight collar, leaning forward while reading a paper in a club type chair, or pressure on the sinus in resting the head on one hand. In carrying out tests for hypersensitivity, patients should be recumbent, and pressure applied first on one side, then on the other, and then bilaterally. Atropine should be ready in a syringe to inject at once if the response is prolonged. Auscultation over the heart and blood pressure should be taken during pressure, and if possible electrocardiograms should be done to record the prevailing rhythm.[21] If hypersensitivity is elicited, the effect of atropine should be observed, and on a later day, the effect of novocainization. If these abolish the reaction, if the sensitivity is marked, and if the spontaneous attacks are frequent and unforeseen, surgical intervention is indicated. Dr. Ray and I have been especially interested in this syndrome.[21] Earlier relief was afforded these patients by denervation of the sinus.[21] Recently Dr. Ray has devised an operation for its cure by the intracranial section of the ninth nerve on the affected side.[22] This syndrome is seen commonly in older individuals with arteriosclerotic changes in the vessels.

*Arteriovenous Aneurysms.* Arteriovenous aneurysms result from trauma, stabbings, or bullet wounds. The diagnostic signs of arteriovenous com-

munications are well known: thrills and bruits over the communication, increase in size of the contiguous vessels, and increase in the size of the part. The heart rate increases; the diastolic blood pressure is low and there is a wide pulse pressure; the circulating blood volume, the volume output of the heart and the heart size, all increase; the circulation time becomes shorter and the venous pressure in the part is elevated.[23]

With surgical closure and elimination of the communication all of these return toward or to their normal levels. Porter has found that an extreme degree of reducible cardiac dilatation can exist over a prolonged period with occurrence of only a minimal amount of cardiac hypertrophy and without the development of heart failure.[23]

*Aneurysm of the Aorta.* The surgical treatment of aneurysms has fascinated surgeons. Aneurysms in certain locations are amenable to ligation. The treatment of aneurysms of the aorta has, however, challenged surgical acumen. In recent years Blakemore and King [24] have reported success in the treatment of aneurysms by the following means: a fine insulated coin-silver wire is introduced through a needle into the aneurysm and passed on and on in and allowed to coil up in the aneurysmal sac. A direct electric current is then passed through the coils in order to encourage coagulation of the blood enmeshed in the coils. In the course of time the whole mass is replaced by fibrous scar tissue.

Recently Alexander and Byron [25] reported the ligation on both sides of and removal of an aneurysm which had developed above the constriction in coarctation of the aorta. In this case collateral channels with reversal of blood flow were already prepared by the congenital defect.

Recently Beck [26] has reported an attempted strengthening of an aneurysm of the left ventricle by the plastering over it and suturing to the edge of the opening made in the pericardium a patch of fascia lata large enough to cover the aneurysm.

*Hypertension.* The treatment of essential hypertension by medical means has not been spectacular or satisfactory. Much can be accomplished symptomatically by helping the individuals to adapt themselves to their problems and life situations, by inculcating the habit of relaxation, and by the moderate use of luminal. However, the course of the disease is rarely interrupted from following its usual patterns with cardiac, renal or cerebral involvement.[27] There has been tremendous interest in hypertension in recent years, and many investigations contributing to an understanding of hypertension have been made. But the fact still remains that the cause of hypertension is not known. Smithwick and others studied sections of the kidney removed at operation and found that no changes were apparent which placed the pathology at this stage in recognizable, anatomical changes in this organ.[28] The most interesting approaches to treatment have been the surgical ones which aim at the interruption of sympathetic nerve pathways. Without tracing the history of these operations it may be stated that the Smithwick procedure is the one which appears to accomplish most in lowering the blood

pressure.[29] The operation is done in two stages. The sympathetic communications are severed first on one side and 10 days to two weeks later on the other side as follows: thoracic 9 to lumbar 2 or 3 inclusive and the greater, lesser and least splanchnic nerves are sectioned.

In a recent lecture at the New York Academy of Medicine before the New York Heart Association, Smithwick reported lowering of blood pressure to normal levels in a large proportion of cases which were subjected to this treatment, and moderate lowering in many others.[30] Further investigation should help in selection of cases which might be expected to respond. Dr. Bronson Ray at the New York Hospital has found significant lowering of blood pressure in a sufficient number of patients from the Smithwick operation to pursue this operative procedure.[30] I have made observations on certain of these patients.[31]

Mention may be made, briefly, of the hypertension associated with pheochromocytoma (adrenal medullary tumor). Fall in blood pressure to normal, decrease in size of the heart, disappearance of the paroxysmal rises in blood pressure with sweating, decrease in basal metabolic rate, and regression of the changes in the eye grounds follow the successful location and removal of a tumor of the medullary portion of an adrenal gland.[32] Exploration of the opposite side should be carried out first before operation, to be certain that the adrenal is normal on that side. It is needless to say that exploration of the adrenals should be made before splanchnic resection for hypertension is carried out.

The status of unilateral nephrectomy for the relief of hypertension which may be associated with disease of one kidney remains to the future.

I have not been convinced of the value of thiocyanate in the lowering of blood pressure.[33] The dangers inherent in its use, namely mental alterations, lethargy, skin eruptions, weakness, nausea and vomiting, induction of goiter, all limit its application. Blood levels should be followed while the drug is being administered.

So-called depressor extracts, garlic and mistletoe, have no place in the treatment of hypertension.

*Angina Pectoris.* The onset of angina pectoris has been viewed gravely by the physician and with great fear by the patient. The reasons for this are several: (1) the grave implication about the state of the coronary vessels and inference from the life histories of other patients, and (2) the great fear of impending death with which the pain may be associated. Patients when free of pain are faced with its recurrence. Much can be accomplished in the care of these patients in reëducation about their activities, slowing down their speed of doing things, care about exertions in cold weather and after meals; nitroglycerine may be used for the acute episodes; aminophyllin 0.1 gm. t.i.d., theobromine and sodium acetate, enteric coated, 0.5 gm. q.i.d., or other vasodilators such as whiskey may be given in the attempt to induce more prolonged and continuous vasodilation. The side effects of nitroglycerine (throbbing and pounding of the heart) may be so disagreeable that some

patients refuse to use it. The frequent use of small doses may eliminate this objection. The use of testosterone and nicotinic acid does not appear to have any place in the treatment of angina. Quinidine 0.2 to 0.3 gm. q.i.d. may be effective [34]; I do not like to give this drug daily, however, over long periods of time. Recently, Freedberg and Riseman [34a] have observed benefit from the use of cobra venom. In many patients these measures are inadequate and other means have been sought. One of the most effective procedures is the interruption of the pain pathways in order to eliminate the pain. This can be done in two ways: the alcohol injection of the posterior root ganglia is one procedure. In some hands, namely White [35] in Boston, and Moore [36] at the Presbyterian Hospital in New York, it has found usefulness. The upper four thoracic ganglia may be injected (or $T_1$ to $T_5$ inclusive). Pleural effusion early and intercostal neuralgia later often make the cure more disagreeable than the disease. Horner's syndrome—enophthalmos, small pupil, drooping of lid and sweating may occur. In uncomplicated cases relief may be of months' and years' duration. If pain is bilateral, one side should be injected at a time.

The second method of interruption of pain sensation is to do posterior root section $T_1$ to $T_5$ on one side or bilaterally if indicated. This has found usefulness in the experience of White [37] and Ray.[38] In Ray's experience he would prefer this operation to alcohol injection and in the cases I have seen in whom Ray has carried out this procedure I have found it effective. On occasions they have recovered so rapidly as to be ambulatory in one week.

There are those who inquire about the wisdom of interrupting the pain signals. The relief which these patients experience from not having pain more than makes up for the academic discussion about this point. Moreover, on severe exertion they have substitution symptoms, discomfort in neck, choking sensation, pain in teeth, which put the brakes on maintaining the activity. They are, of course, cautioned about exertion as before operation and urged to limit it to what they can do without distress. Patients should not be chosen for this operation who have evidence of too marked damage to the heart muscle or who have had recent coronary occlusion, or who have heart failure.

There are several operations which are designed to increase the blood supply to the heart muscle. Beck [39] has tried pectoral muscle transplant and the production of adhesions by artificial means to bring in a new blood supply. O'Shaughnessy [40] brought vascular-rich omentum through an opening in the diaphragm and sutured it to the heart muscle. Thompson [41] has induced adhesions by the use of powder blown into the pericardial cavity. All of these measures are in the investigative stage and large numbers of patients should not be subjected to these procedures until further investigation has been made and the course of those already treated is known.

Another approach to the problem has been through the reduction of metabolic demands of the human organism by total ablation of the thyroid gland.[42] It is said to be effective in selected cases. More recently Raab has

reported [43] improvements in angina patients with the reduction of the basal metabolic rate from the administration of thiouracil. If this procedure proves effective and safe, it will avoid the disadvantages of a permanent defect brought about by surgical ablation of the thyroid gland.

The cervical rib and the scalenus anticus syndromes may be mentioned briefly. Pain in these syndromes may be confused with angina pectoris especially when the discomfort is on the left side. Relief may follow removal of the offending rib or cutting the muscle which encroaches upon the artery or brachial plexus. If hiatus hernia is the cause of pain, relief often follows from frequent small feedings and use of tincture of belladonna. A patient should not be treated for years for angina only to find later that he has hiatus hernia, spontaneous interstitial emphysema,[44] or ruptured thoracic disc. The exercise test, carried out with electrocardiographic records, and the Levy anoxemia test [45] are useful procedures in the differential diagnosis of angina pectoris.

*Treatment of the Irregularities of the Heart.* On the whole, I think irregularities of the heart have been managed in a more satisfactory manner in recent years.[46] What can be accomplished in the treatment of irregularities, per se, beyond the treatment of the underlying cause may be summarized as follows:

*A.* Premature Contractions: (1) Attention should not be directed to premature contractions if the patient is not aware of them. (2) When premature contractions give rise to symptoms, relief may be secured, frequently, by the use of small doses of triple bromide. (3) Auricular premature contractions may disappear on digitalization. (4) Ventricular premature contractions may occasionally require the use of quinidine.

*B.* Paroxysmal Tachycardia: (1) Supraventricular paroxysmal tachycardia may respond to simple measures like holding the breath, carotid sinus pressure, etc. (2) Mecholyl may cause cessation of supraventricular paroxysmal tachycardia. (3) Digitalization is the most satisfactory drug for treatment of auricular or nodal paroxysmal tachycardia. (4) Quinidine should be used for ventricular paroxysmal tachycardia. Digitalis should not be used in this rhythm and electrocardiograms should be taken when possible to be certain of the rhythm.

*C.* Auricular Flutter: (1) Digitalization will cause reversion to normal rhythm in most instances and is the drug of choice.

*D.* Auricular Fibrillation: (1) Digitalis should be used to keep the ventricular rate slow. (2) The following factors are to be considered in evaluation of the use of quinidine to cause reversion: (*a*) if the size of the heart is large, (*b*) if the duration of fibrillation is long, (*c*) if heart failure is present, quinidine should not be used for this purpose.

*E.* Stokes-Adams Syndrome: (1) Patients should be taught to live within their capabilities. (2) Adrenalin 1 c.c., 1:1000 solution, subcutaneously is the most effective drug. (3) I have recently seen complete heart block disappear with the use of ephedrine 20 mg. t.i.d.

*Arteriosclerotic Heart Disease.* Certain changes take place in the heart muscle and vessels with aging which occur early in some individuals and later in others. There are no means known of slowing the progression of these changes, aside from a rational mode of living and eating and engaging in activities. After the onset of symptoms referable to the heart, such as heart failure or angina, in this etiological group patients are treated by the means which are mentioned under those headings. By and large these patients have a longer, more comfortable and more useful life span ahead of them now than before the introduction of the mercurial diuretics.

*Coronary Occlusion.* What have we to offer the patient who has a coronary occlusion? With proper care I think the outlook need not be too depressing. Many patients return to full activity with some of their useless activities eliminated. It can be made a time for the individual to reassess his activities, aims in life, etc., and it has been my experience that these patients have often gone back to their profession or work with a clearer course, and a period of greater effectiveness than was theirs before this accident. I begin early in the attack to use the illness and convalescence as a period of reëducation from the point of view of the years to come. The acute period and the months afterward are the most important from the long time angle. I advocate the early use of oxygen when there are cyanosis and dyspnea and pain; I do not use vasodilator drugs except whiskey, and occasionally aminophyllin. There should be an adequate period of complete rest in bed, four to six to eight weeks or longer, depending on the severity and complications. During this time the bed pan is used; patients are fed; moderate, passive and then active movements of legs are made to prevent stasis; the position of body is shifted; breathing deeply several times a day expands the lungs; toward the end of the complete rest the head is propped up and then gradually the patient is brought to the sitting position, allowed to read, etc. Then, in order, very gradual sitting up, walking, lavatory privileges, bath, etc., requiring a month or more in getting to this stage; then gradual resuming activities one after the other, taking around five to six months before going back to work; and then gradual resumption of work. How much activity is finally attained depends upon the patient's cardiac reserve, economic status, interests, etc., and has to be carefully worked out with the patient. After about one year he is on his own again except for the periodic check-ups. In making these recommendations I am not unaware of the problems of the general practitioner, and realize how difficult it is to have patients adhere to this régime. Electrocardiograms aid in prognosis, since the anterior apex lesions have a somewhat more serious prognosis than do the posterior base ones.[47]

There is inadequate evidence offered by those who would have us treat coronary occlusion in an ambulatory or semiambulatory way to take this form of therapy seriously.[48, 49] The analogy between working a striated muscle to increase its blood supply and working the heart muscle in an area of which the blood supply is interrupted in a heart in which the arteries are

sclerotic and not normal, is not valid. Patients who have ignored the early symptoms of coronary occlusion, and have kept going, have done less well in my experience.

*Rheumatic Heart Disease.* What is the present status of what we can accomplish in rheumatic fever?

First, with respect to recurrences of rheumatic infection: there is nothing at present which can be offered the whole population of rheumatic fever patients to prevent recurrences. The use of sulfa drugs and perhaps eventually of penicillin to prevent streptococcal and respiratory infections has very interesting and far-reaching possibilities. The time is not yet ripe, in private practice, for putting patients on the drug with these objectives because the blood counts should be checked so frequently and blood levels of the drug followed. However, if anyone is interested in observing a series and keeping adequate records for the detection of toxicity, he should be encouraged. One gram of the drug a day appears to be adequate. Blood dyscrasias have been occasionally described in patients already subjected to this routine.[50] Increased impetus has been given to this problem by the studies made in the Army Air Force by Holbrook [51]; in this series there was a reduction in the incidence of rheumatic infection with the control of streptococcal infections with sulfadiazine. Proof of the prevention of recurrences by salicylates does not appear to be convincing enough to warrant their use. The prevention of recurrences by living in the tropics is applicable to the treatment of a relatively small number of patients.[52]

What can be done in the treatment of rheumatic patients with heart disease aside from the problem of recurrences: (1) Have the subject live a sane life, avoiding over exertion, etc. (2) Teach respect for colds and sore throats, advising bed rest during these episodes. Caution patient to avoid crowds in winter. (3) Use of sulfonamides before and after tooth extractions and tonsillectomies in order to prevent implantation of organisms causing subacute bacterial endocarditis. Sulfadiazine, 1.0 gm., together with soda bicarbonate 2.4 gm., q. 4 h. for the 24 hours before operation, the day of operation, and 48 hours after the procedure is recommended. If penicillin orally comes up to the early expectations, it may supplant sulfadiazine for this purpose. (4) The treatment and cure of subacute bacterial endocarditis with penicillin will be mentioned later. (5) Once the symptoms and signs of heart failure have appeared, there is now a more cheerful outlook with adequate treatment of failure so that maintenance of an adequate circulation over a longer time than was formerly to be expected is now possible.

*Luetic Heart Disease.* It is too early to estimate the effect which penicillin therapy will have on the incidence of luetic heart disease in later years.

*Heart Failure.* The onset of heart failure until fairly recently was viewed gloomily by physicians and patients. Digitalis was prescribed in a haphazard way, usually a few drops a day. As there was not spectacular improvement, the use of digitalis in the lay mind connoted the last stage of

their disease. The general principles of treatment of heart failure are the same whatever the etiological and anatomical background, whether rheumatic, arteriosclerotic, hypertensive, etc. Due to many factors the patient who has developed heart failure can now look forward to many years of usefulness with varying degrees of restriction of activities. The most important development, it seems to me, was the introduction of the mercurial diuretics. Next, and almost as important, has been the more intelligent use of digitalis. The general understanding is that larger amounts of digitalis must be given to get an adequate therapeutic effect, for instance, 1.8 gm. New York Heart Association preparation of digitalis may be given in 24 hours when the patient has not had digitalis within two weeks. The continued use of this drug by maintenance doses, the restriction of fluid intake to 1,200 c.c. q.d., and salt intake to 2 gm. q.d., the other adjuncts such as ammonium chloride, urea, and the restriction of the patient's activities after recovering from heart failure to what he can do without a recurrence, all contribute to maintenance of compensation. The most important phase of treatment of heart failure comes after recovery. It is still not uncommon to see all medication stopped after recovery and the patient allowed to resume the same amount of activity. It is much more important to prevent recurrence of failure than to treat each recurrence with the lessened capacity to restoration. After recovery from heart failure there should be slow convalescence, continuation usually of digitalis, continued use of mercupurin on every third day or at weekly intervals, continued restriction of fluid and salt intake, and adequate care about setting the level of the patient's activities. Today our cardiac patients continue to come to the clinic one to two times a week for years and years after the first onset of heart failure. Hazards in these patients are respiratory infections, especially acute bronchitis with the increased load on the heart; these should be treated with complete rest in bed, steam inhalations, often oxygen, etc. The treatment of heart failure by the use of large amounts of water and the acid ash diet as described by Schemm,[52a] requires further study before its use is widely advocated.

*Thyroid Heart Disease.* The appearance of cardiac complications in hyperthyroidism is well recognized. I am not referring to such manifestations as slight breathlessness and tachycardia, palpitation, rise in systolic blood pressure which are a part of the clinical picture. I refer to the appearance of auricular fibrillation, auricular flutter and heart failure. With the prolonged increase in basal metabolic rate the circulation is overburdened; there may be increase in breathlessness, râles, and all gradations of insufficiency up to marked congestive heart failure which does not differ in its clinical manifestations from other etiological types of failure. The treatment of decompensation is the same as in other patients with failure: namely, restriction of fluids to 1,200–1,500 c.c. q.d., low salt intake, full digitalization (1.8 gm. New York Heart Association preparation in 24 hours), mercupurin 2 c.c. intravenously every third day, oxygen tent if necessary; vitamin supplement may be used because there may have been depletion by the excessive

metabolic rate. If auricular fibrillation is present, it may require more than the usual amount to slow the ventricular rate, because of the increased basal rate. With the use of iodine (1 c.c. t.i.d. Lugol's solution or syrup of hydriodic acid) the heart rate slows, the symptoms regress, the patient gains weight, and there is reduction in the basal metabolic rate. There is with the use of all these measures reason to expect reduction or complete clearing of the signs and symptoms of heart failure and the patient can be made ready for operation. It is my custom to continue the use of maintenance amounts of digitalis in these patients through and past the postoperative period. In the presence of normal rhythm, at an appropriate time in convalescence if all has gone well, the reasons for further use are examined. If the rhythm is auricular fibrillation, I usually wait for some weeks after operation and in many, normal rhythm will recur spontaneously while digitalis is continued. If it persists the use of quinidine is considered, taking into account the absence or presence of heart failure, size of heart, duration of fibrillation.

In any patient in whom the onset of auricular fibrillation is not adequately explained, or in a patient with rheumatic heart disease with auricular fibrillation in whom the ventricular rate begins to be uncontrolled by the usual amounts of digitalis, with slight temperature rises, the onset of hyperthyroidism should be suspected. With close working together of surgeon and physician cardiac patients or hyperthyroid patients who have had heart failure can be safely carried through two stages of thyroidectomy under local or ether-oxygen anesthesia.

The place of thiouracil (1.0 gm. q.d. on the average) in the treatment of Graves' disease remains to be decided.[53] Careful observations of the white blood count should be made when the drug is being used. At the present time, in my opinion, it should not be used in complicated cases with cardiac manifestations. I think these patients can be managed better at present with iodine and operation until the effects of thiouracil are more clearly defined.

*Myxedema Heart.* The clinical picture of typical myxedema is easily recognized: the thick juicy, pasty skin, the pallor of the thick lips, the slowed down appearance, the mental dullness and slow speech, the cold skin,[54] coarse sparse hair, associated with a low basal metabolic rate, a high blood cholesterol, increased size of the cardiac shadow, a slow heart rate, and a history of gain in weight. The electrocardiogram shows low amplitude of the QRS–T waves, with varying degrees of auriculoventricular heart block.[55] The cardiac output in these patients is low per minute and per beat, the circulation time prolonged, the heart large, and the venous pressure usually normal.[55] With the administration of thyroid extract the patient improves objectively and subjectively. The basal metabolic rate increases, the heart shrinks in size, the cardiac output increases, and the circulation time becomes shorter, and the auriculoventricular block decreases and disappears.[55] These changes are reversible and can be made to swing in either direction by the use of or discontinuance of thyroid extract. The changes in heart size

are slower in taking place. We are very careful to give thyroid extract in small amounts and increase it gradually. For example to one of our patients we gave 0.015 gm. on February 24, increased to 0.03 gm. on March 3, to 0.06 gm. on March 7, to 0.10 gm. on March 15, to 0.12 gm. on March 21, and to 0.18 gm. on March 23. There is reason for not suddenly whipping up the circulation when it has been retarded for years. The danger of coronary occlusion in patients in this age group when demand is put on the circulation by increasing the metabolic requirements is very real.

*Beriberi Heart.* The occurrence of cardiac manifestations may be a part of vitamin $B_1$ deficiency, but clearcut instances of the so-called beriberi heart, such as were formerly encountered in the Orient, are not seen frequently. In this part of the country it is encountered as a part of chronic alcoholism associated with restricted food intake. There is enlargement of the heart with peripheral vasodilatation and moderate to generalized edema; the serum proteins may be low. Rapid arm to tongue circulation time in the presence of increase in venous pressure helps to differentiate this from the other types of heart failure.[56] The amplitude of the QRS complexes in the electrocardiogram may be decreased and occasionally there is negativity of $T_1$. Prompt and rapid amelioration of all the signs and symptoms follows the daily administration of thiamin hydrochloride 50–100 mg. intravenously. Other measures such as use of whole wheat bread, lean meat, fresh vegetables, brewer's yeast may be instituted. If beriberi heart disease is suspected, digitalis and other diuretics should not be used not only because they are ineffective but also because they cloud the picture in making a correct diagnosis by the therapeutic test with thiamin.

*Anemia.* The cardiac embarrassment which may occur in severe anemia disappears with the increase in the red blood count and hemoglobin and restoration of the serum proteins.

*Acute Nephritis.* Occasionally heart failure may occur in acute nephritis and regress when the usual régime used in the treatment of heart failure is instituted.

*Acute Cor Pulmonale.* The acute embarrassment of the circulation which occurs with pulmonary infarction or overloading the heart with fluids is reversible. The clinical signs disappear and there is regression of certain typical electrocardiographic patterns which have been described in acute cor pulmonale.[57, 58]

*Thrombophlebitis and Pulmonary Infarction.* The treatment of thrombophlebitis has taken on new interest. The complications of thrombophlebitis which are feared are the formation of saddle thrombus, and of embolization to the lungs with a large embolus or with showers of emboli. When thrombophlebitis occurs in the leg veins, there are those who advocate prompt ligation of the vein under local anesthesia.[59] One of the most interesting advances in this field is in the use of anticoagulants. Heparin 30 to 40 mg. per hour in saline or 5 per cent glucose may be given by continuous intravenous drip, care being exercised to keep the clotting time within 20 to

30 minutes (not more than one hour). It may be kept up for one week to 10 days. It is best to use a concentrated solution so that not more than 1 liter of fluid is required in 24 hours. Prompt decrease in the swelling of the part results and the patient who was having repeated showers of pulmonary emboli recovers. I have had no experience with the use of dicoumarin as a substitute for heparin. Its effects are induced less rapidly and having been initiated they are less easily controlled because they are of longer duration, namely, one to five days. Its effect on the prothrombin time is observed.

It is my practice to attempt first the usual treatment of rest and elevation of the part with local dry heat, and if regression occurs, to maintain this régime. If, however, there is progression, use of the other measures is considered.

*Arterial Occlusions.* There is not a uniformity of opinion about the treatment of acute arterial occlusions and different surgeons seeing the same patient will recommend different procedures. If the patient is seen early and the vessel is large, embolectomy is to be considered. The other measures are the use of the Pavex boot, rocking bed, papaverine hydrochloride, 0.064 gm. q. 4 h. and lumbar paravertebral block of 2–3–4 with novocaine.[60] All of these measures are designed to enlarge the arterial blood supply and to promote the formation of collateral circulation. Without operation or nerve block I have seen return of excellent function from use of the Pavex boot and later, perseverance on the part of the patient in the use of the extremity.

*Subacute Bacterial Endocarditis.* I have reserved subacute bacterial endocarditis for final consideration. Until recently, after many years in Internal Medicine, I had yet to see a proved case of subacute bacterial endocarditis recover. One of the most encouraging gains in therapeutics in many years has been in the treatment of subacute bacterial endocarditis with penicillin. The use of sulfonamides often lowered the temperature and brought about sterilization of the blood stream for varying lengths of time. Recent analyses by White and Kelson [61, 62] as well as the experience of others has shown that very little was accomplished and its use has been abandoned. On the other hand, the results which have been reported from the use of penicillin are very encouraging,[63] and additional reports are appearing rapidly from many clinics. With proper treatment, *at least* 50 per cent or more of early cases of subacute bacterial endocarditis are cured. It is too early, however, to have gained any definite notion about what the percentage of cures will ultimately be, and what the life history of those cured will be. The diagnosis should be substantiated by positive blood culture and tests should be made to assay the sensitivity of the strain of organism to penicillin. If it is sensitive, penicillin should be given. Rapid strides are being made in the technic of penicillin therapy and routines of therapy have not become shaped. It appears at present that 300,000 to 400,000 units daily, given q. 2 h., intramuscularly day and night continued for several weeks is the technic of choice. There is little evidence that anything is gained by

giving heparin simultaneously, as described by Loewe. Extremely large doses up to 1,000,000 or 5,000,000 units a day may be required to sterilize the blood stream. After recovery from subacute bacterial endocarditis the underlying heart disease remains with its implications.

## Summary

In evaluating the present status of the treatment of cardiac diseases we find that we are in a period of rapid advancement. Advances have been contributed by surgical measures for treating cardiac abnormalities, and by new chemotherapeutic measures and new drugs and refinements in the use of other well known drugs. Moreover, there is still room for the continued utilization of the art of medicine in the management of sick individuals. Patients with hopeless congenital cardiac defects, formerly thought beyond relief, are now restored to normal health; patients with hearts restricted by encasement in unyielding fibrous tissue which may be calcified, with progressive invalidism facing them, are restored to normal activity; patients with the hopeless prognosis of subacute bacterial endocarditis are apparently cured; and patients who have heart failure now maintain an effective cardiac reserve with the intelligent use of digitalis and mercurial diuretics and attain a longer, more comfortable and more useful life span. These triumphs, to recapitulate only a few, give us ample encouragement to look to the future with confidence that further advances are to be expected.

## BIBLIOGRAPHY

1. Gross, R. E., and Hubbard, J. P.: Surgical ligation of patent ductus arteriosus: report of first successful case, Jr. Am. Med. Assoc., 1939, cxii, 729.
2. Gross, R. E.: Surgical management of patent ductus arteriosus: with summary of four surgically treated cases, Ann. Surg., 1939, cx, 321.
3. Gross, R. E.: Complete surgical division of the patent ductus arteriosus: report of fourteen successful cases, Surg., Gynec., and Obst., 1944, lxxviii, 36.
3a. Gross, R. E., and Hufnagel, C. A.: Coarctation of the aorta, New England Jr. Med., 1945, ccxxxiii, 287.
4. Shapiro, M. J., and Keys, Ancel: The prognosis of untreated patent ductus arteriosus and the results of surgical intervention, Am. Jr. Med. Sci., 1943, ccvi, 174.
5. Hubbard, J. P., Emerson, P. W., and Green, H.: Indications for the surgical ligation of a patent ductus arteriosus, New England Jr. Med., 1939, ccxxi, 481.
6. Touroff, A. S. W., and Vesell, H.: Subacute *Streptococcus viridans* endarteritis complicating patent ductus arteriosus, Jr. Am. Med. Assoc., 1940, cxv, 1270.
7. Blalock, A., and Taussig, H. B.: The surgical treatment of malformation of the heart in which there is pulmonary stenosis or pulmonary atresia, Jr. Am. Med. Assoc., 1945, cxxviii, 189.
8. Stewart, H. J., and Bailey, R. L., Jr.: The cardiac output and other measurements of the circulation in coarctation of the aorta, Jr. Clin Invest., 1941, xx, 145.
9. Stewart, H. J., Haskell, H. S., and Evans, W. F.: The peripheral blood flow and other observations in coarctation of the aorta, Am. Heart Jr., 1944, xxviii, 217.
10. Goldburgh, H. L., and Baer, S.: Death following the intravenous administration of diodrast, Jr. Am. Med. Assoc., 1942, cxviii, 1051.

11. Churchill, E. D.: Pericardial resection in chronic constrictive pericarditis, Ann. Surg., 1936, civ, 516.
12. Heuer, G. J., and Stewart, H. J.: The surgical treatment of chronic constrictive pericarditis, Surg., Gynec., and Obst., 1939, lxviii, 979.
13. Stewart, H. J., and Heuer, G. J.: Chronic constrictive pericarditis. Dynamics of the circulation and results of surgical treatment, Arch. Int. Med., 1939, lxiii, 504.
14. Heuer, G. J., and Stewart, H. J.: The surgical treatment of chronic constrictive pericarditis, New York State Jr. Med., 1945, xlv, 993.
15. Beck, C. S., and Griswold, R. A.: Pericardiectomy in treatment of Pick's syndrome, Arch. Surg., 1930, xxi, 1064.
16. Blalock, A., and Burwell, C. S.: Chronic constrictive pericarditis, Jr. Am. Med. Assoc., 1938, xxi, 265.
17. Harrington, S. W.: Chronic constrictive pericarditis; partial pericardiectomy and epicardiolepis in twenty-four cases, Ann. Surg., 1944, cxx, 468.
18. Stewart, H. J., Carty, J. R., and Seal, J. R.: Contributions of roentgenology to the diagnosis of chronic constrictive pericarditis, Am. Jr. Roentgenol., 1943, xlix, 349.
19. Stewart, H. J., Heuer, G. J., Deitrick, J. E., Crane, N. F., Watson, R. F., and Wheeler, C. H.: Measurements of the circulation in constrictive pericarditis before and after resection of the pericardium, Jr. Clin. Invest., 1938, xxvii, 581.
20. Weiss, S., Capps, R. B., Jr., Ferris, E. B., Jr., and Munro, D.: Syncope and convulsions due to hyperactive carotid sinus reflex; diagnosis and treatment, Arch. Int. Med., 1936, lviii, 407.
21. Ray, B. S., and Stewart, H. J.: Observations and surgical aspects of the carotid sinus reflex in man, Surgery, 1942, ii, 915.
22. Ray, B. S., and Stewart, H. J.: Treatment of hypersensitive carotid sinus by glossopharyngeal nerve section, Trans. Harvey Cushing Soc. Jr. Neurosurg., 1944, i, 338.
23. Porter, W. B., and Baker, J. P.: The significance of cardiac enlargement caused by arteriovenous fistula, Ann. Int. Med., 1937, ii, 370.
24. Blakemore, A. H., and King, B. G.: Electrothermic coagulation of aortic aneurysms, Jr. Am. Med. Assoc., 1938, cxi, 1821.
25. Alexander, J., and Byron, F. X.: Aortectomy for thoracic aneurysm, Jr. Am. Med. Assoc., 1944, cxxvi, 1139.
26. Beck, C. S.: Operation for aneurysm of the heart, Ann. Surg., 1944, cxx, 34.
27. Stewart, H. J.: The management of hypertension, Bull. New York Acad. Med., 1938, xiv, 681.
28. Castleman, B., and Smithwick, R. H.: The relation of vascular disease to the hypertensive state based on a study of renal biopsies from one hundred hypertensive patients, Jr. Am. Med. Assoc., 1943, cxxi, 1256.
29. Smithwick, R. H.: Technique for splanchnic resection for hypertension: preliminary report, Surgery, 1940, vii, 1.
30. Smithwick, R. H.: The surgical treatment of hypertension. Scientific Session. New York Heart Assoc., New York Acad. Med., Jan. 26, 1945. Discussion by Bronson S. Ray.
31. Stewart, H. J., Evans W. F., Haskell, H. S., and Brown, H.: The effect of splanchnic resection on the peripheral blood flow, rectal and skin temperatures in hypertension, In press, Am. Heart Jr.
32. Evans, W. F., and Stewart, H. J.: The peripheral blood flow in a case of adrenal pheochromocytoma before and after operation, Am. Heart Jr., 1942, xxiv, 835.
33. Fanson, E., Kinsey, D., and Palmer, R. S.: Potassium sulfocyanate therapy in essential hypertension, New England Jr. Med., 1943, ccxxix, 540.
34. Riseman, J. E. F.: The treatment of angina pectoris. A summary of ten years' objective study, New England Jr. Med., 1943, ccxxix, 670.
34a. Freedberg, A. S., and Riseman, J. E. F.: Cobra venom in the treatment of angina pectoris, New England Jr. Med., 1945, ccxxxiii, 462.

35. White, J. C., and White, P. D.: Angina pectoris: treatment with paravertebral alcohol injections, Jr. Am. Med. Assoc., 1928, xc, 1099.
36. Levy, R. L., and Moore, R. L.: Paravertebral sympathetic block with alcohol for the relief of cardiac pain, Jr. Am. Med. Assoc., 1941, cxvi, 2563.
37. White, J. C.: Paravertebral injections of alcohol, ganglionectomy and posterior rhizotomy for the relief of cardiac pain. "Diseases of the coronary arteries and cardiac pain" by Robert L. Levy, 1936, The Macmillan Co., New York, p. 363.
38. Ray, B. S.: Personal Communication.
39. Feil, H., and Beck, C. S.: Coronary sclerosis and angina pectoris. Report of thirty patients treated by the Beck operation, Jr. Thoracic Surg., 1941, x, 529.
40. O'Shaughnessy, L.: Surgical treatment of cardiac ischaemia, Lancet, 1937, i, 185.
41. Thompson, S. A., and Raisbeck, M. J.: Cardio-pericardiopexy; the surgical treatment of coronary arterial disease by the establishment of adhesive pericarditis, Ann. Int. Med., 1942, xvi, 495.
42. Berlin, D. D., Riseman, J. E. F., and Blumgart, H. L.: Present status of total thyroidectomy: review of seven and one half years' experience, Trans. Am. Assoc. Study Goiter, 1940, pp. 1–6.
43. Raab, W.: Thiouracil treatment of angina pectoris, Jr. Am. Med. Assoc., 1945, cxxviii, 249.
44. Hamman, L.: Spontaneous mediastinal emphysema, Bull. Johns Hopkins Hosp., 1939, lxiv, 1.
45. Patterson, J. E., Clark, T. W., and Levy, R. L.: A comparison of electrocardiographic changes observed during the "anoxemia test" on normal persons and on patients with coronary sclerosis, Am. Heart Jr., 1941, xxiii, 837.
46. Stewart, H. J.: Functional disorders of the heart. Cardiac arrhythmias. Cecil's Textbook of medicine, 6th ed., 1943, W. B. Saunders, Philadelphia, p. 1111.
47. Baer, S., and Frankel, H.: Studies in acute myocardial infarction. III. Diagnosis and location of the infarct by electrocardiogram, Arch. Int. Med., 1944, lxxiii, 286.
48. Thomas, W. C., and Harrison, T. R.: The effect of artificial restriction of activity on the recovery of rats from experimental myocardial injury, Am. Jr. Med. Sci., 1944, ccviii, 436.
49. Jetter, W. W., and White, P.D.: Rupture of the heart in patients in mental institutions, Ann. Int. Med., 1944, xxi, 783.
50. Thomas, C. B.: The prophylactic treatment of rheumatic fever by sulfanilamide, Bull. New York Acad. Med., 1942, xviii, 508.
51. Holbrook, P. W.: The Army Air Forces rheumatic fever control program, Jr. Am. Med. Assoc., 1944, cxxvi, 84.
52. Coburn, A. F.: The factor of infection in the rheumatic state, 1931, The Williams and Wilkins Co., Baltimore, p. 122.
52a. Schemm, F. R.: A high fluid intake in the management of edema, especially cardiac edema. I. The details and basis of the regime, Ann. Int. Med., 1942, xvii, 952.
53. Barr, D. P.: The medical management of thyrotoxicosis, Surgery, 1944, xvi, 668.
54. Stewart, H. J., and Evans, W. F.: Peripheral blood flow in myxedema, Arch. Int. Med., 1942, lxix, 808.
55. Stewart, H. J., Deitrick, J. E., and Crane, N. F.: Studies of the circulation in patients suffering from spontaneous myxedema, Jr. Clin. Invest., 1938, xxvii, 237.
56. Jolliffe, N., and Rosenblum, L. A.: Circulatory manifestations of vitamin deficiency: diagnosis, treatment and prevention, Med. Clin. N. Am., New York Number, May 1939.
57. McGinn, S., and White, P. D.: Acute cor pulmonale resulting from pulmonary embolism. Its clinical recognition, Jr. Am. Med. Assoc., 1935, civ, 1473.
58. Stewart, H. J., Kirk, R. C., and Smith, J. J.: Electrocardiographic changes in pulmonary infarction, Series III, New Internat. Clin., 1940, iii, 135.

59. HOMANS, J.: Exploration and division of the femoral and iliac veins in the treatment of thrombophlebitis of the leg, New England Jr. Med., 1941, ccxxiv, 179.
60. DURYEE, A. W.: The management of peripheral vascular disease, Bull. New York Acad. Med., 1943, xix, 478.
61. KELSON, S. R., and WHITE, P. D.: Notes on 250 cases of subacute bacterial (streptococcal) endocarditis studied and treated between 1927 and 1939, Ann. Int. Med., 1945, xxii, 40.
62. WHITE, P. D., MATHEWS, M. W., and EVANS, E.: Notes on the treatment of subacute bacterial endocarditis encountered in 88 cases at the Massachusetts General Hospital during the six year period 1939 to 1944 (inclusive), Ann. Int. Med., 1945, xxii, 61.
63. DAWSON, M. H., and HUNTER, T. H.: The treatment of subacute bacterial endocarditis with penicillin, Jr. Am. Med. Assoc., 1945, cxxvii, 129.

# AN APPARATUS FOR THE INTRODUCTION OF PENICILLIN AEROSOL INTO THE NASAL ACCESSORY SINUSES WITH A CASE REPORT OF A PATIENT WITH CHRONIC SINUSITIS *

By Alvan L. Barach, M.D., F.A.C.P., Bettina Garthwaite, M.D., Max Soroka, B.S., and Frederick F. Anderson, *New York, N. Y.*

In a preliminary report [1] the inhalation of nebulized penicillin in bronchopulmonary infections was described. In some instances the mist of penicillin was inhaled through the nose with the idea that the sinuses might be in communication with the air in the nasal passages. However, in order to introduce penicillin aerosol into the sinuses, it was finally considered necessary to evacuate air from the sinuses by developing a negative pressure in the nasal passages with immediate replacement of air containing penicillin in high concentrations.† ‡

An apparatus was devised for production of penicillin aerosol with intermittent negative pressure in the nasal and postnasal pharynx. A glass venturi tube was inserted in the rubber tubing from the oxygen cylinder. The lower end of the venturi tube was connected by rubber tubing to the reinhalational nebulizer. With a liter flow from the oxygen regulator set between 6 to 12 liters per minute a satisfactory production of penicillin aerosol is obtained. The horizontal glass tube of the venturi is connected to a positive and negative pressure valve (figure 1). The purpose of this especially constructed valve is to allow the passage of oxygen through the nebulizing apparatus when the handle is in the upright position and to develop a negative pressure in the nose pieces when the handle is in the horizontal position. When suction is being produced in the nasal cavities oxygen flows through an aperture in the valve and is prevented from going through the nebulizer. When the handle of the valve is turned to the upright position a negative pressure in the nasal cavities is stopped and the oxygen stream is then diverted to the nebulizer reinhalation apparatus. The details

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The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

This research was aided by a grant from the Josiah Macy, Jr. Foundation.

† We are indebted to Dr. George Foster Herben for suggesting the preliminary use of suction in combination with the penicillin reinhalation apparatus.

‡ Reduced atmospheric pressure in a low pressure chamber has been used with favorable results to provide effective suction and increase aeration of the sinuses and promote drainage.[2] During the period when air reënters the nasal accessory sinuses no antibiotic substance was used in this procedure.

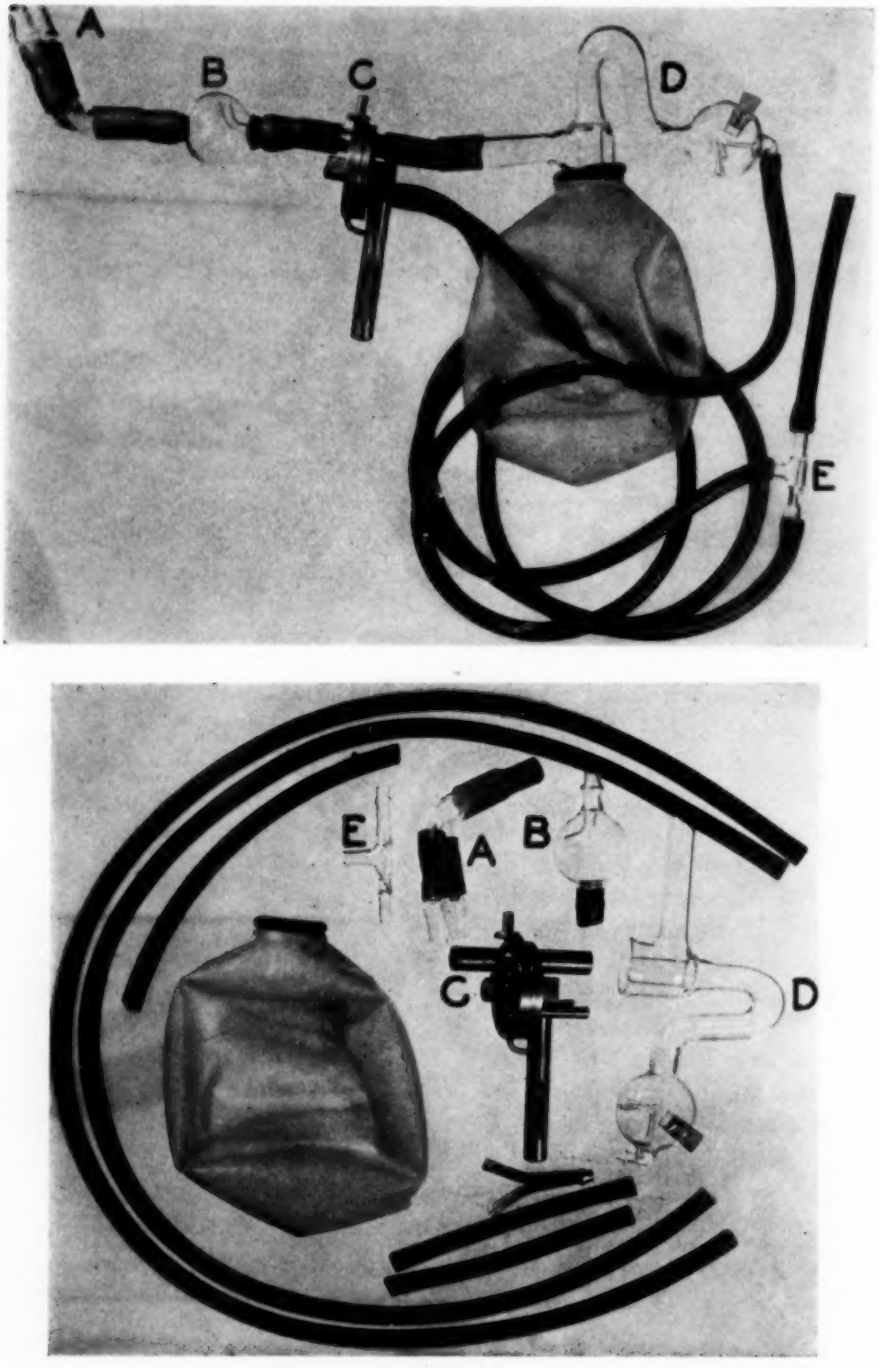


FIG. 1. A reinhalational nebulizer apparatus with a positive and negative pressure valve attachment for the introduction of penicillin aerosol into the nasal accessory sinuses: (A) Nose piece, (B) glass trap for collection of nasal secretions, (C) special valve for provision of positive and negative pressures; horizontal position produces suction, upright position connects nebulizing apparatus with nose piece for inhalation of penicillin, (D) reinhalational nebulizer, (E) venturi tube for production of negative pressure.

of the mechanism of the positive and negative pressure valve are illustrated in figure 2.

Although the conventional positive and negative pressure nose and throat apparatus may be employed with the special valve illustrated above (figure 2), the glass venturi tube inserted in the tubing from the oxygen cylinder produces completely adequate suction as well as positive pressure and has the advantage of use by the patient in his own room. The degree of negative pressure obtained at the orifices of the nasal attachment depends on the rate of flow of oxygen through the venturi tube. As will be seen in table 1 negative pressures of considerable degree are produced when the oxygen flow is between 7 and 10 liters per minute.

POSITIVE AND NEGATIVE
PRESSURE VALVE

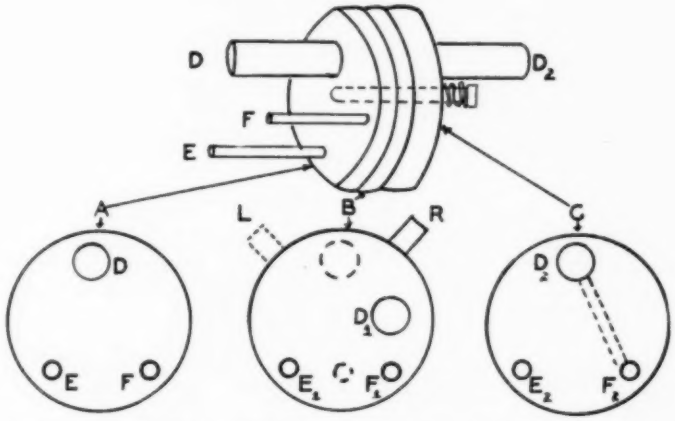


FIG. 2. Positive and negative pressure valve. The valve consists of three discs A, B, and C held together by a spring and having three holes D, E, and F. The outer discs are yoked together and the center disc B may be rotated 30°. Positive pressure leads are attached to D and E. Negative pressure lead is attached to F. $D_2$ is attached to nose piece. When center disc is moved to left hand position D, $D_1$ and $D_2$ are in line and E and F are occluded. When center disc is moved to right hand position E lines up with $E_1$ and $E_2$, F with $F_1$ and $F_2$ and D is occluded. In this position negative pressure is applied to $D_2$ through a channel from $F_2$.

The purpose of this procedure is to introduce air containing penicillin into the nasal accessory sinuses after partial evacuation of air or secretions from the sinuses have been obtained by negative pressure in the nasal passages. At the start of a treatment the nose pieces are fitted snugly into the nose, the handle of the special valve is turned upward and the oxygen flow set to 8 liters per minute. The patient then breathes penicillin aerosol for one to three minutes. The solution employed consists of a concentration of 20,000 to 25,000 units of penicillin per c.c. of normal saline. Since the nebulizer employed produces particles of small size, the majority of which are under 1 micron in diameter, the mist is relatively stable and does not quickly condense in the rebreathing bag.* After a preliminary period of inhalation

* The reinhalation nebulizer has been made from the Vaponefrin type nebulizer.

of penicillin nebulin through the nose has been performed the handle of the special valve is turned downward and the patient is instructed to say K–K–K until a definite suction effect is experienced. In our experience swallowing has been more effective in producing a negative pressure in the nasal passages than the use of the K maneuver. After several suction effects have been obtained the handle of the valve is turned to the upright position and penicillin aerosol is again inhaled. This procedure is repeated until 2 c.c. of the solution has been nebulized. In this way repeated evacuation of air from the sinuses and replacement with air containing a mist of penicillin is produced. During the phase of negative pressure the Eustachian tube may be opened in those cases in which previous obstruction has been present.

Previous shrinkage of the mucous membrane of the nose may be obtained with either neosynephrine or privine. In addition the nasal passages may be

TABLE I

Negative Pressure Produced by Oxygen Flow Through Venturi Tube

| Oxygen Flow, Liters per Minute | Negative Pressure, cm. Hg |
|---|---|
| 3½ | 2 |
| 4½ | 4 |
| 5½ | 6 |
| 6½ | 8 |
| 7½ | 11 |
| 8½ | 14 |
| 9 | 16 |
| 10 | 18.2 |
| 11 | 21 |
| 12 | 22 |
| 13 | 23.4 |
| 14 | 24.4 |
| 15 | 26 |

first cleansed by washing with normal saline or saline containing penicillin, 500 U/c.c. Neither of these procedures is generally used.

In order to prevent secretions from the nose entering the valve a glass trap has been inserted between the nose piece and the valve.

The number of treatments with intermittent negative pressure and penicillin aerosol inhalation will have to be determined by experience and the indications of the individual patient. In previous investigations of bronchopulmonary infections an inhalation of 50,000 units, at times 100,000 units, in 1 c.c. normal saline, was employed four to five times daily, often in conjunction with an oral dose of 100,000 units of penicillin at bedtime and during the middle of the night. The dosage of penicillin in the therapy of chronic pan-sinusitis requires considerable further investigation.*

* In hospital practice, four treatments are given daily, 40,000 units of penicillin in 2 c.c. normal saline. When the patient breathes through the mouth during the nebulization of penicillin, a more dense mist is present in the nasal passages. A single daily treatment has been used in office treatment, generally 50,000 units in 2.5 c.c. normal saline. The nebulizer should be rinsed three times with 0.5 c.c. normal saline, in order to dissolve the penicillin that clings to the glass walls of the nebulizer. This solution is then nebulized, with intermittent negative pressure.

The purpose of this report is to present a method by which a negative pressure may be produced in the nasal cavity that might accomplish drainage and partial evacuation of air in the accessory nasal sinuses, and in addition introduce penicillin aerosol into the sinus cavities themselves. Although a concentration of 50,000 units per c.c. would be irritating if applied locally in a solution, the provision of this concentration in the form of a nebulin exercises a different effect since particles of 1 micron or less lodge on the mucous membrane of the nose or sinuses and are immediately surrounded by a fluid medium that swiftly results in a dilute concentration. Calcium penicillin has been found to be better tolerated and much less apt to cause irritation than the sodium salt.

The following case was treated by a combination of orally administered penicillin and intermittent negative pressure with penicillin aerosol inhalations.

## Case Report

*History.* A 15 year old white school boy had a history of chronic sinusitis dating back to infancy, following an attack of bilateral acute otitis media with spontaneous perforation of both drums. A second episode occurred at the age of two and one-half years with accompanying mastoiditis not requiring surgery. Since that time the patient had had chronic purulent nasal and aural discharge. Two years previous to admission, following a severe case of measles, he developed bilateral deafness which persisted for two months and left some permanent impairment. Adenoidectomy was performed at the age of 11 months, tonsillectomy and adenoidectomy at the ages of 7 and 13 years. For many years the patient had undergone frequent ear, nose and throat treatments with antral irrigations and inflation of the Eustachian tubes with little improvement. His complaints on admission were impaired hearing, nasal discharge with stuffy sensations, occasional non-productive cough, easy fatigability, and four pounds weight loss in recent months. He denied headaches, otalgia and fever.

*Physical Examination.* The patient was a well-developed, fairly well-nourished white youth not appearing ill. Temperature 98.6° F., pulse 80, respirations 20, blood pressure 108 mm. Hg systolic and 70 mm. diastolic. Positive findings were limited to ear, nose and throat examination. Nose revealed slight deviation of the septum to the left, a boggy congested mucosa with a small amount of mucopurulent discharge in both nostrils and hypertrophy of the inferior turbinates. There was obvious impairment of hearing, more marked on the right. Bone conduction was greater than air conduction. Weber test did not lateralize. There was slight yellowish discharge filling the external auditory meatus bilaterally. Pharynx appeared moderately reddened. The posterior cervical lymph nodes were slightly enlarged but non-tender.

*Laboratory Data.* Hemoglobin 14.8 gm., red blood cells 5.2, white blood cells 5,700 with polymorphonuclears 46 (0–6–40), lymphocytes 46, monocytes 7, eosinophiles 1. Sedimentation rate 5 mm./hr. Sputum culture: *Staphylococcus albus* predominating. Nasal culture: no growth. Sinus roentgenograms revealed clear frontals, bilateral clouding of the ethmoid cells, marked thickening of the lining membrane of both maxillary antra with homogeneous density in the lower half suggesting fluid present, and peripheral clouding of the sphenoids suggesting thickened lining membrane (figure 3, left).

*Course.* The patient remained afebrile throughout his two weeks' stay and was ambulatory. He was treated with a course of oral sodium penicillin, 100,000 units

mixed with 10 c.c. amphojel five times daily, receiving a total of 5,900,000 units. Calcium penicillin aerosol was administered by nasal inhalation using the alternating negative and positive pressure apparatus with a dosage of 50,000 units in 1 c.c. normal saline two to three times daily for a total of 1,100,000 units. No other drugs or therapy were employed. By the third day of this regimen the patient noted marked improvement which was sustained. Nasal discharge practically disappeared and the mucosa appeared healthy. There was concomitant improvement in hearing and the patient's general sense of well-being. Sinus roentgenograms after one week of treatment showed definite clearing of the ethmoid and antral sinuses, although some thickening of the antral lining membranes persisted. Sinus films 11 days after the

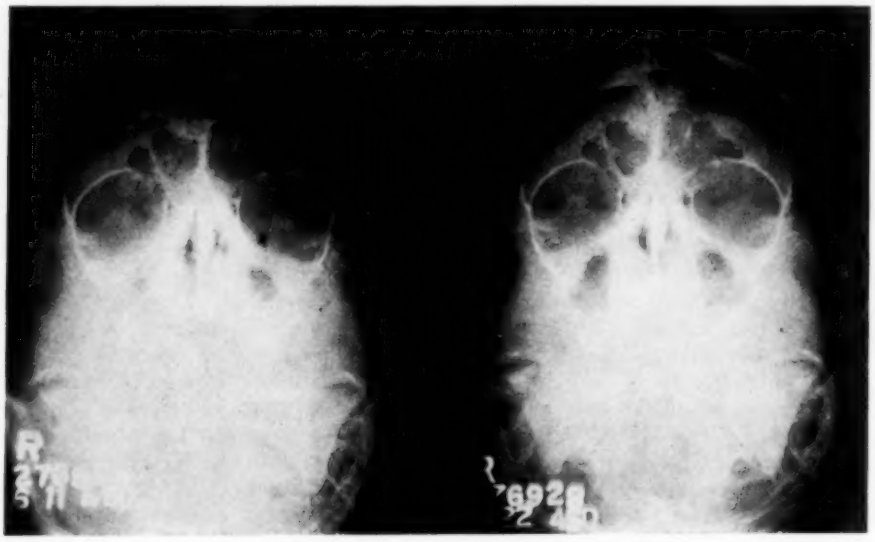

FIG. 3. Roentgen-ray examination of the sinuses before treatment (June 11, 1945) revealed bilateral clouding of the ethmoid cells, marked thickening of the lining membrane of both maxillary antra with homogeneous density in the lower half suggesting a fluid level and peripheral clouding of the sphenoids suggesting thickened lining membrane. Sinus films 11 days after the onset of therapy (June 22, 1945) showed definite clearing of the ethmoid and antral sinuses with no evidence of retained fluid.

onset of therapy showed further improvement in appearance of maxillary antra and ethmoid cells with no evidence of retained fluid (figure 3, right). Throat culture following treatment revealed *B. acrogenes* predominating. The patient was discharged from the hospital markedly improved.* †

* This patient remained entirely well, without nasal discharge, for eight months. Although he then developed an acute coryza, he recovered without flare-up of sinus infection. Subsequent roentgenograms showed no sinus disease. His hearing and general health are much improved.

In four other cases of severe sinus disease, nebulized penicillin with negative pressure resulted in clearing of the infection, without the use of oral or systemic administration of penicillin. Our more recent experience is highly encouraging, suggesting that the procedure described above is not only a valuable therapeutic aid in the treatment of sinusitis, but one that is free from pain and trauma and easily carried out in the office, hospital or home.

† The negative pressure valve set-up used in the treatment of sinusitis may be obtained from F. F. Anderson & Co., 4652 Spuyten Duyvil Parkway, New York, 63, N. Y.

## Summary

An apparatus is described which provides: (1) negative pressure in the nasal passages and nasal accessory sinuses, (2) inhalation of nebulized penicillin, and (3) partial evacuation of air from the sinuses and replacement with penicillin aerosol.

A venturi tube attached to the oxygen regulator produces an adequate negative pressure when a flow of 6 to 10 liters per minute of oxygen is used.

A specially constructed valve, attached to a reinhalation nebulizer, makes possible alternate inhalation of penicillin aerosol and suction-pressure in the nasal cavities and accessory sinuses.

A case of chronic sinusitis is reported in which marked improvement took place following a combination of orally administered penicillin and intermittent negative pressure with penicillin aerosol inhalations.

## BIBLIOGRAPHY

1. Barach, A. L., Silberstein, F. H., Oppenheimer, E. T., Hunter, T., and Soroka, M.: Inhalation of penicillin aerosol in patients with bronchial asthma, chronic bronchitis, bronchiectasis and lung abscess, Ann. Int. Med., 1945, xxii, 485.
2. Andrews, A. H., Roth, L. W., and Ivy, A. C.: On the use of reduced atmospheric pressure in the treatment of paranasal sinusitis, Quart. Bull., 1941, xv, 46.

# CASE REPORTS

## ACUTE HEMOLYTIC ANEMIA DUE TO NEOARSPHENAMINE: REPORT OF A FATAL CASE *

By Lawrence E. Young, M.D., William N. Valentine, Lieutenant, M.C., A.U.S., and Joe W. Howland, Lieutenant, M.C., A.U.S.

A case of fatal hemolytic jaundice following injection of neoarsphenamine is described in this report. No descriptions of similar reactions can be found in the literature.

Moore [1] states that "the relative rarity of the blood dyscrasias due to the arsenical drugs is fortunate, since they are among the gravest of treatment complications." He points out that in more than half of the reported cases the blood picture was that of aplastic anemia and 80 per cent of these patients died. Farley [2] expresses the belief that all blood dyscrasias after arsphenamine therapy are manifestations of varying degrees of depressed bone marrow activity. Although aplastic anemia, agranulocytosis and thrombocytopenia have been repeatedly described as complications of the arsenical treatment of syphilis, there is to the best of our knowledge, no record of the occurrence of hemolytic anemia after the administration of any of the arsphenamines.

Dameshek and Schwartz [3] list arsphenamine and neoarsphenamine among the causes of hemolytic anemia but give no reference to specific cases. Dameshek [4] does not cite any specific instances of hemolytic reaction following arsenotherapy, and this type of hematologic complication is not mentioned in the reviews of Loveman,[5] McCarthy and Wilson,[6] Hahn,[7] Phelps,[8] and Probey et al.[9] Carter, Chambers and Anderson,[10] in their report of 1,153 reactions after 1,900,000 doses of arsenicals, describe a case in which death followed injection of silver arsphenamine. The autopsy diagnoses include multiple hemorrhages, aplastic anemia and acquired hemolytic jaundice. However, no clinical or pathological data are given to support the diagnosis of hemolytic jaundice. The liver is described as being browner than normal and having "indistinct internal markings" but no mention is made of the findings in the blood serum or urine (other than hematuria). The blood picture presented is that of aplastic anemia.

The case described in this paper is presumably the first of its kind to be reported.

### Case Report

F. G., a 54 year old Italian male, was admitted to the Strong Memorial Hospital at 1:00 a.m., July 31, 1943. Three hours before admission he had been given 0.4 gm. neoarsphenamine intravenously by his private physician. Five minutes after receiving the injection he became violently dizzy and had severe chilly sensations. When he reached home he vomited twice and then began to have severe pain in the lower back.

* Received for publication October 31, 1944.

From the Department of Medicine, The University of Rochester School of Medicine and Dentistry and the Medical Clinic of the Strong Memorial Hospital.

He was then seen by his physician, given adrenalin without relief, and sent to the hospital.

The past history with reference to syphilis and antisyphilitic therapy is summarized in table 1. He received his first injection of neoarsphenamine in 1940 and the second and third injections on July 9 and 16, 1943, without reaction. The fourth dose of neoarsphenamine was given July 23, 1943, and was followed immediately by chills and fever and a 12 hour episode of nausea and vomiting. During the next week he was apparently normal and worked as usual. The symptoms described above followed the fifth injection of neoarsphenamine on July 30, 1943.

TABLE I

Luetic History of Case Reported

| Date | Number of Injections of Anti-luetic Drugs[1] | | | | Reactions to Therapy | Serological Tests of Blood for Syphilis | |
|---|---|---|---|---|---|---|---|
| | Bismuth[2] | Arsphenamine[3] | Neoarsphenamine | Mapharsen[4] | | Wassermann[5] | Kahn |
| 1924 | History of Penile Chancre | | | | | | |
| 1928 | | | | | | 4+ | 3+ |
| 1928–1934 | Type of Treatment Unknown | | | | | | |
| 1934–1940 | 90 | 80 | | | Chills and Fever for 3 Days after Bi Injection in 1940 | 2+ | 4+ |
| Dec. 7, 1940 | | | 0.2 Gm. | | None | | |
| Dec. 14, 1940 to April 1941 | | | | 15 | None | − | + |
| Feb. 6, 1943 | | | | 1 | None | Spinal Fluid Negative | |
| Mar. 1943 to July 1943 | 8 | | | | None | | |
| July 9, 1943 | | | 0.1 Gm. | | None | | |
| July 16, 1943 | | | 0.2 Gm. | | None | | |
| July 23, 1943 | | | 0.3 Gm. | | 12 Hour Episode of Chills, Fever, Nausea and Vomiting Starting Immediately after Injection | | |
| July 30, 1943 | | | 0.4 Gm. | | Acute Hemolytic Reaction | | |
| August 1, 1943 | Autopsy: Syphilis of Aorta and Aortic Valve | | | | | | |

[1] All anti-luetic therapy was administered outside the Strong Memorial Hospital.
[2] Bismuth subsalicylate 0.13 gm. in 1.0 c.c. peanut oil intramuscularly.
[3] Arsphenamine dosage: 0.2 to 0.4 gm. intravenously.
[4] Mapharsen dosage: 0.02 to 0.03 gm. intravenously.
[5] Cholesterinized antigen.

*Physical Examination.* On admission the temperature was 103° F., pulse 160, respirations 28 per minute, blood pressure 90 mm. Hg systolic and 55 mm. diastolic. The patient appeared acutely ill and the skin was hot, dry and flushed but no rash was present. The tongue was dry and partially coated with blood that appeared to have oozed from the gums. Cardiac findings were normal except for marked tachycardia. The lungs were clear. Abdominal and neurological examinations were negative. A penile scar was present.

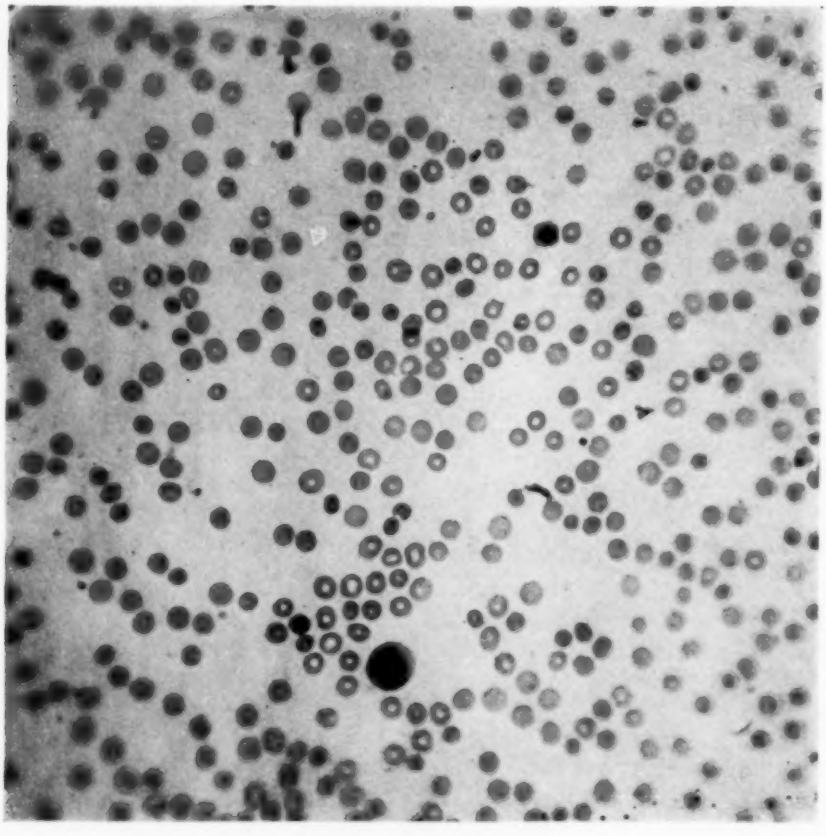

FIG. 1. Blood smear showing an undifferentiated white cell, two normoblasts, moderate anisocytosis of the red cells, and a few spherocytes.

*Laboratory Findings.* The urine was reddish brown, contained many golden brown granular casts, a few white blood cells but no red blood cells. The guaiac test for hemoglobin, and the heat and acetic acid test for albumin were strongly positive. The foam test for bilirubin was negative.

The blood plasma was reddish brown and had a hemoglobin content of 370 mg. per 100 c.c. The icterus index was 40, carbon dioxide combining power 35 volumes per cent, non-protein nitrogen 47 mg., albumin 4.2 grams and globulin 1.8 grams per 100 c.c. The red blood cell count on admission was 3.5 million,* white blood cell count 4,800, hemoglobin 13.4 gm., reticulocyte count 3 per cent. A blood smear

* A possible explanation of the relatively high red blood cell count may be found in the presence of the shock state with its known hemoconcentration.

(figure 1) prepared at 1:00 p.m. on July 31 and stained with Wright's stain showed moderate anisocytosis, and slight poikilocytosis. A few spherocytes were seen. The average red cell size was estimated to be normal. There was some stippling and diffuse basophilia of the red cells, and 10 normoblasts per 100 white cells were counted. Platelets were present in normal numbers. No toxic granules were seen in the neutrophiles, but there was a shift to the left and an eosinophilia of 8 per cent. A differential count of 200 white cells was as follows:

| | | | |
|---|---|---|---|
| Basophiles | 0.5% | Stab cells | 24.0% |
| Eosinophiles | 8.0% | Filamented cells | 10.0% |
| Myelocytes | 1.5% | Lymphocytes | 34.5% |
| Juveniles | 20.0% | Monocytes | 1.5% |

The results of the erythrocyte fragility test (hypotonic saline) are given below.

| | Per Cent Sodium Chloride Giving Indicated Degree of Hemolysis | | |
|---|---|---|---|
| | Beginning | Marked | Complete |
| Patient | 0.52% | 0.40% | 0.30% |
| Control | 0.48% | 0.40% | 0.32% |

Tests for cold agglutinins, cold hemolysins (Donath-Landsteiner) and warm hemolysins were negative. Attempts to demonstrate hemolysis of the patient's cells in

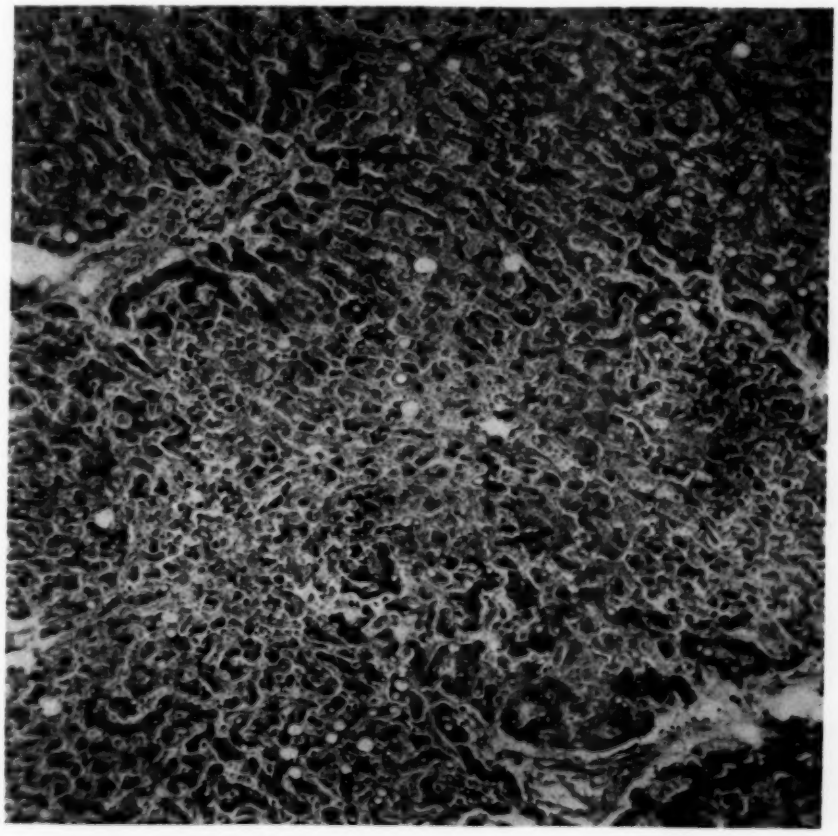

FIG. 2. Section of liver showing focal necrosis and vacuolization of liver cells.

mixtures of compatible normal serum and various amounts of neoarsphenamine were unsuccessful.

*Course in the Hospital.* During the patient's 24-hour stay in the hospital only 80 c.c. of urine could be obtained by catheterization. The temperature remained elevated and the blood pressure rose to 116 mm. Hg systolic and 80 mm. diastolic a few hours after admission, but later fell to 70 mm. systolic and 60 mm. diastolic and could not be obtained during the last half hour of life. Within 12 hours after admission the sclerae became icteric and the liver was palpable.

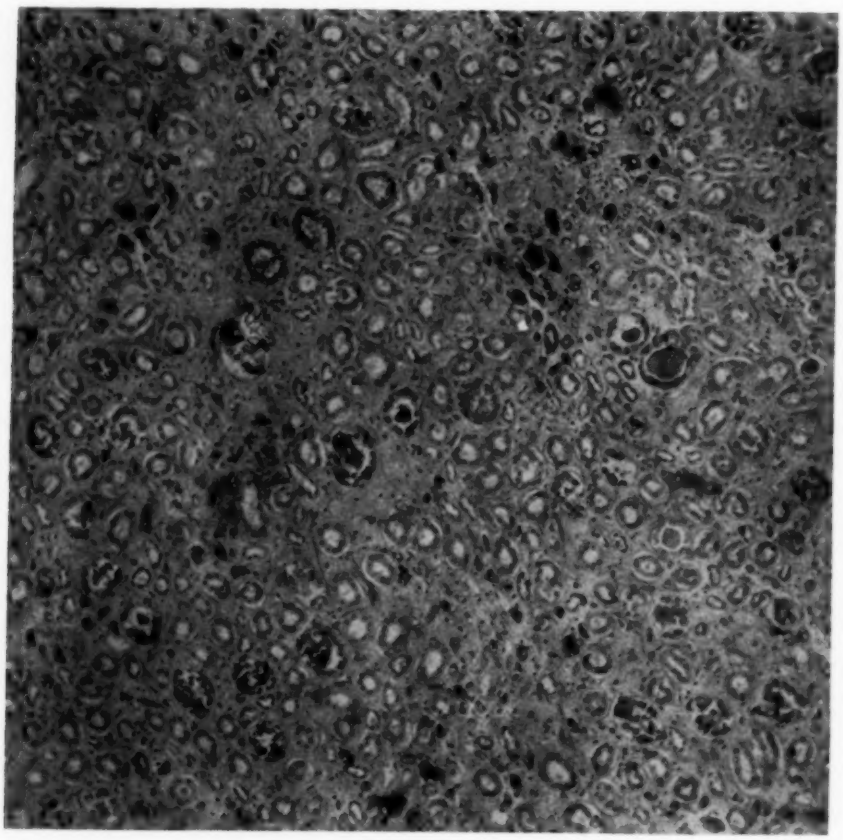

FIG. 3. Section of kidney. Hemoglobin casts are present in some of the collecting tubules.

Therapy consisted of sodium lactate, dextrose and blood plasma given intravenously in an attempt to promote diuresis and combat shock. Pulmonary congestion developed terminally and the patient became dyspneic, cyanotic and died at 1:20 a.m., August 1, 1943. The necessary vigorous intravenous therapy undoubtedly contributed to the development of the terminal pulmonary edema.

*Autopsy Findings.* There was minimal syphilitic involvement of the aorta and aortic valve. Hydrothorax and pulmonary congestion and edema were present bilaterally. In the liver (figure 2) were focal areas of hyaline necrosis and infiltration with neutrophilic granulocytes. Some of these areas were located centrally, some peripherally in the lobule; most of them occupied about one-third to one-half of a

lobule but some replaced an entire lobule. The other liver cells contained an increased number of large and small vacuoles.

The spleen was intensely congested and there were numerous polymorphonuclear leukocytes in the red pulp. There was dense infiltration of the adrenal medulla with lymphocytes and a few polymorphonuclear cells.

The convoluted tubules of the kidney showed cloudy swelling in some areas; in others the tubular cells were entirely degenerated and only granular, pink-staining material remained in the tubule. Some of the collecting tubules contained hemoglobin casts (figure 3).

The bone marrow showed a moderate degree of normoblastic hyperplasia.

## Discussion

Further consideration of this case involves the answers to two questions.

1. Was the fatal illness caused by the injection of neoarsphenamine or was it merely coincidental? It should be emphasized that a milder but unmistakable reaction occurred immediately after the fourth injection of the drug one week prior to admission and that symptoms of the fatal reaction began within five minutes after receiving the fifth and last injection. This sequence of events and the eosinophilia of 8 per cent suggest a specific sensitization as the basis for the reaction. In view of this history and the fact that other drugs of similar chemical composition are known to cause hemolytic anemia,[3] the conclusion that death was due to neoarsphenamine seems reasonable.

The question might be raised as to the presence of a subclinical form of congenital hemolytic jaundice with a crisis precipitated by the drug. Against this remote possibility are the lack of significant increase in fragility of the erythrocytes in hypotonic saline, the absence of hemosiderosis in the liver and spleen, and the negative history of jaundice and anemia in other members of the family. With regard to the presence of spherocytes in the patient's blood smear, it can only be said that these cells are found in acquired hemolytic anemia as well as in the congenital type.[8]

2. Was the anemia truly hemolytic in nature? The hemoglobinemia and hemoglobinuria indicate that red cells were being destroyed rapidly. Accelerated activity of the marrow was clearly shown by slight reticulocytosis, basophilia of the erythrocytes, normoblastic hyperplasia of the marrow and the presence of normoblasts in the peripheral blood, as well as by the shift to the left in the granulocytes. It is clear that this was not a case of aplastic anemia. It is well known that most of the drugs capable of causing hemolysis in vivo do not do so in the test tube. Hence, it is not surprising that all of the tests for hemolysis performed were negative.

The renal lesions are similar to those described after acute hemolytic reactions from a variety of causes, including the transfusion of incompatible blood.[11] Although severe renal damage after arsenotherapy in the absence of excessive blood destruction has been described,[1, 7] it seems more likely that the pathologic changes seen in this case were caused by the hemolytic reaction rather than by any direct toxic effect of the neoarsphenamine itself.

Two explanations of the mechanism by which focal necrosis of the liver was produced seem reasonable. (1) Lesions similar to those shown in figure 2 have been observed in patients suffering from hemolytic processes of various types.[11, 12] That some product of the rapid destruction of erythrocytes may cause this injury

is also suggested by the studies of Hawkins et al.[13] who repeatedly observed necrosis of the liver followed by death in dogs injected intravenously with alkaline hematin solutions. (2) It is known that the arsphenamines themselves are capable of producing all degrees of parenchymatous hepatic degeneration.[1, 14] Although it is obviously impossible to solve the mystery of pathogenesis of the hepatic lesions in this case, it is probably fair to state that the patient's jaundice was of the hemolytic or "retention" type rather than "regurgitative" [15] because of the absence of bilirubin in the urine. Another type of postarsphenamine jaundice can therefore be added to the list of those previously described.[14, 16, 17, 18]

## Summary

A case of fatal hemolytic anemia following the fifth injection of neoarsphenamine is described. No earlier reports are known.

The hepatic and renal lesions appear to be the result of the hemolytic reaction rather than of the toxicity of the neoarsphenamine.

Hemolytic jaundice should be included in the classification of postarsphenamine jaundice.

The authors are indebted to Dr. John S. Lawrence, Dr. William B. Hawkins and Dr. Sidney C. Madden for assistance in the preparation of this report.

## BIBLIOGRAPHY

1. Moore, J. E.: The modern treatment of syphilis, second edition, 1941, C. C. Thomas, Springfield, Illinois.
2. Farley, D. L.: Depressed bone marrow function from the arsphenamines, Am. Jr. Med. Sci., 1930, clxxix, 214.
3. Dameshek, W., and Schwartz, S. O.: Acute hemolytic anemia, Medicine, 1940, xix, 231.
4. Dameshek, W.: Personal communication, 1944.
5. Loveman, A. B.: Toxic granulocytopenia, purpura hemorrhagica and aplastic anemia following the arsphenamines, Ann. Int. Med., 1932, v, 1238.
6. McCarthy, F. P., and Wilson, R., Jr.: The blood dyscrasias following the arsphenamines, Jr. Am. Med. Assoc., 1932, xcix, 1557.
7. Hahn, R. D.: Antisyphilitic treatment: mortality studies, a clinical, statistical, and pathologic analysis of 47 fatal reactions, Am. Jr. Syph., Gonor., and Ven. Dis., 1941, xxv, 659.
8. Phelps, J. R.: Reactions incidental to the administration of 191,778 doses of neoarsphenamine and other arsenical compounds in the United States Navy, U. S. Nav. Med. Bull., 1929, xxvii, 205.
9. Probey, T. F., Norris, E. W., Deibert, A. V., and Price, E. V.: Sulfarsphenamine in the therapy of syphilis. A comparative study of the toxic manifestations of neoarsphenamine and sulfarsphenamine, Pub. Health Rep., 1944, lix, 733.
10. Carter, T. J., Chambers, W. M., and Anderson, L. T.: Toxic effects of arsenical compounds, U. S. Nav. Med. Bull., 1944, xlii, 229.
11. Wiener, A. S.: Blood groups and transfusion, third edition, 1943, C. C. Thomas, Springfield, Illinois.
12. Farrar, G. E., Jr., Burnett, W. E., and Steigman, A. J.: Hemolysinic anemia and hepatic degeneration cured by splenectomy, Am. Jr. Med. Sci., 1940, cc, 164.
13. Hawkins, W. B., Mann, F. D., and Strain, W. H.: Unpublished observations.
14. Soffer, L. J.: Postarsphenamine jaundice, Am. Jr. Syph., Gonor., and Ven. Dis., 1937, xxi, 309.

15. Rich, A. R.: The pathogenesis of the forms of jaundice, Bull. Johns Hopkins Hosp., 1930, xlvii, 338.
16. Hanger, F. M., and Gutman, A. B.: Postarsphenamine jaundice apparently due to obstruction of intrahepatic biliary tract, Jr. Am. Med. Assoc., 1940, cxv, 263.
17. Salaman, M. H., King, A. J., Williams, D. I., and Nicol, C. S.: Prevention of jaundice resulting from antisyphilitic treatment, Lancet, 1944, ii, 7.
18. Sheehan, H. L.: Epidemiology of infective hepatitis, Lancet, 1944, ii, 8.

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## THE SYNDROME OF COMPRESSION OF THE PULMONARY ARTERY BY A SYPHILITIC AORTIC ANEURYSM WITH OR WITHOUT ARTERIO-ARTERIAL COMMUNICATION *

By I. C. Brill, M.D., F.A.C.P., and R. S. Jones, M.D., *Portland, Oregon*

It is well-known that simple syphilitic aortic aneurysm imposes no appreciable strain on the heart. If heart failure supervenes it is usually found to be due either to involvement of the aortic valve or to narrowing of the coronary ostia. In both these instances the strain is predominantly on the left ventricle and is recognized clinically by left-sided enlargement with aortic configuration and electrocardiographic changes denoting left ventricular preponderance.

A much rarer complication of aortic aneurysm is compression of the pulmonary artery with or without arterio-arterial communication. The cardiac strain in this instance is predominantly of the right ventricle. The rarity of this complication is evident from the fact that up to the present time (1944) only 86 cases have been recorded in the literature, of which only six were recognized during life. For detailed reports of these cases together with a review of the literature, the reader is referred to recent publications by Garvin and Siegel,[1] White, Chamberlain and Kelson,[2] Porter,[3] Schattenberg and Harris,[4] and Nicholson.[5]

The purpose of this communication is to place on record an additional case diagnosed during life and to point out two possible sets of symptoms and signs the recognition of which should permit more frequent clinical diagnosis of the condition.

### Case Report

F. G., a white laborer, aged 52 years at the time of his death in January, 1944, was first seen in the Out-Patient Clinic 10 years previously (September, 1933) for an acute upper respiratory infection. A history was obtained of an untreated penile sore contracted at the age of 18 and the blood showed a four plus Wassermann reaction. Physical examination revealed no noteworthy changes; the heart was normal in size and shape and the cardiac sounds were unaltered. The patient was treated intensively with bismuth and neoarsphenamine from September, 1933, to October, 1939, during which period several physical examinations revealed no significant changes until April 6, 1937, when a "distant diastolic murmur along the lower left sternal border" was found. On that same day fluoroscopic examination showed no cardiac enlargement and the aortic shadow was considered normal.

* Received for publication February 19, 1945.
From the Departments of Medicine and Pathology of the University of Oregon Medical School.

Early in 1943 the patient began to complain of precordial pain and dyspnea and in June (1943) fluoroscopic examination revealed dilatation of the base of the ascending aorta with marked increase in the pulmonary hilar shadows which extended downward and obscured the outline of the diaphragm.

A roentgenogram of the chest, taken on July 6, 1943, was described as follows: "The cardiac shadow is partially obscured by densities which extend outward from

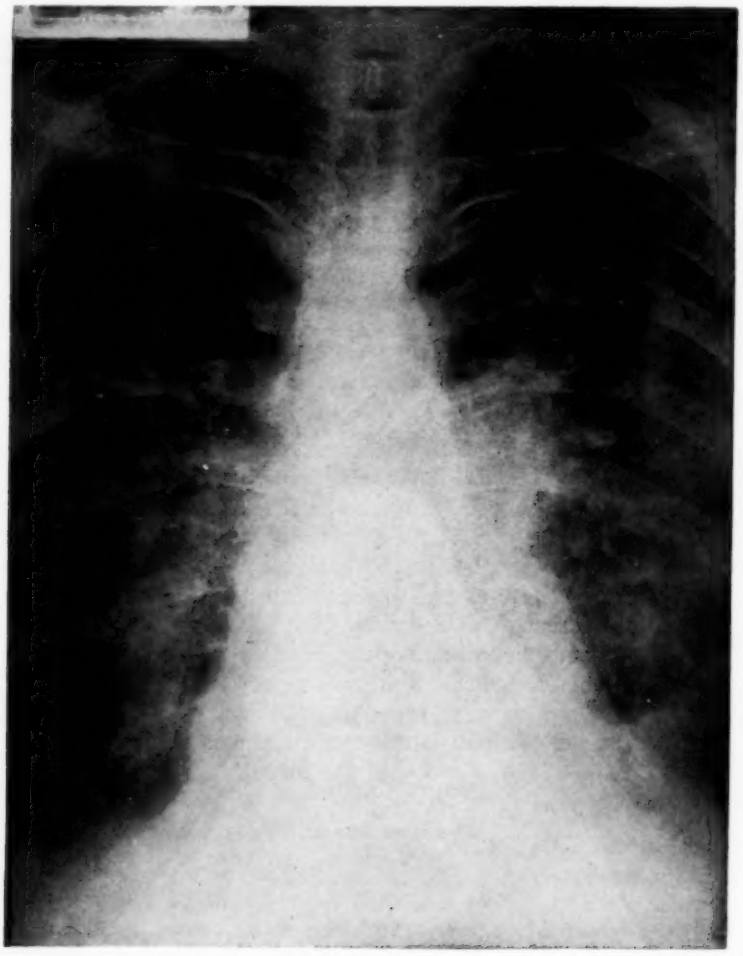


FIG. 1. Roentgenogram of chest taken July 6, 1943, showing enlargement of pulmonary artery shadows at both hilar areas which more or less obscure the outline of the cardiac silhouette. Curved linear calcifications are seen to extend on either side of the eighth to tenth dorsal vertebrae suggesting the presence of an aneurysm of the ascending aorta.

both hilar shadows into the inner two-thirds of the lung fields. Both pulmonary artery shadows appear to be enlarged. These densities in the lung fields extend down to both leaves of the diaphragm and fade out in the outer zones of the chest. Extending to either side of the eighth, ninth, and tenth dorsal vertebrae are two curved linear calcifications, approximately 4 cm. in length. The aortic knob also contains a rim of calcium. It is most likely that the curved linear densities represent an

aneurysm of the descending aorta. The heart shows moderate generalized enlargement."

Fluoroscopically there was seen slight motion in the calcified walls of the aneurysm. The hilar shadows showed exaggerated motion. Both leaves of the diaphragm moved normally.

Another film taken one month later (August 12, 1943) showed some further

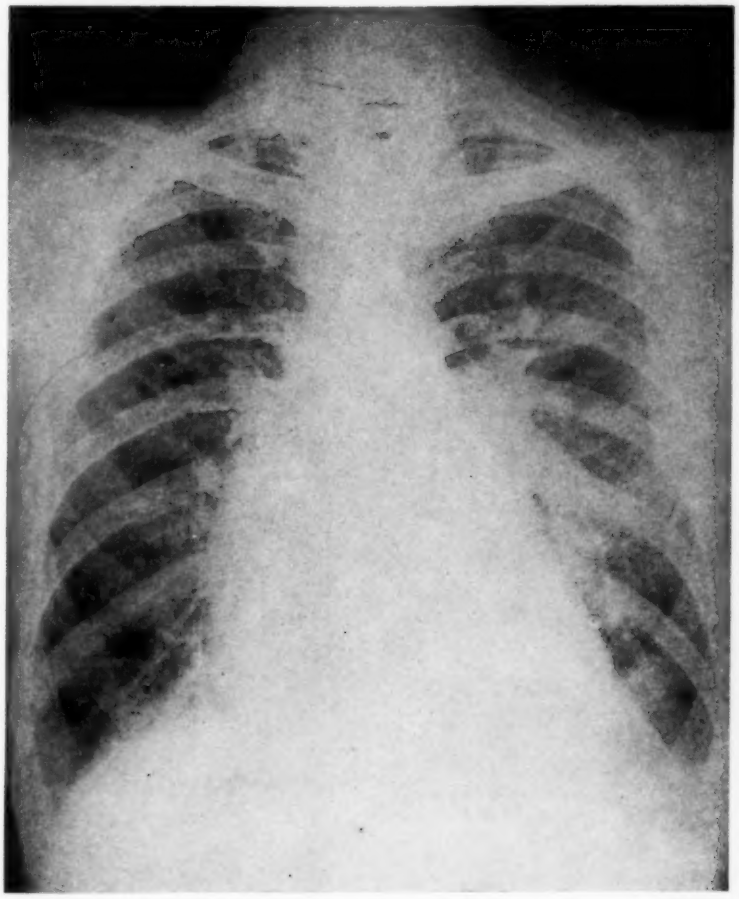


FIG. 2. Roentgenogram of chest taken August 12, 1943, showing more advanced changes in the cardio-pulmonary shadows suggesting the presence of cor pulmonale.

enlargement of the cardiac shadow and a relatively larger increase in the hilar densities.

Electrocardiograms taken on August 16 and October 8, 1943, showed a progressively increasing right axis deviation and right ventricular strain.

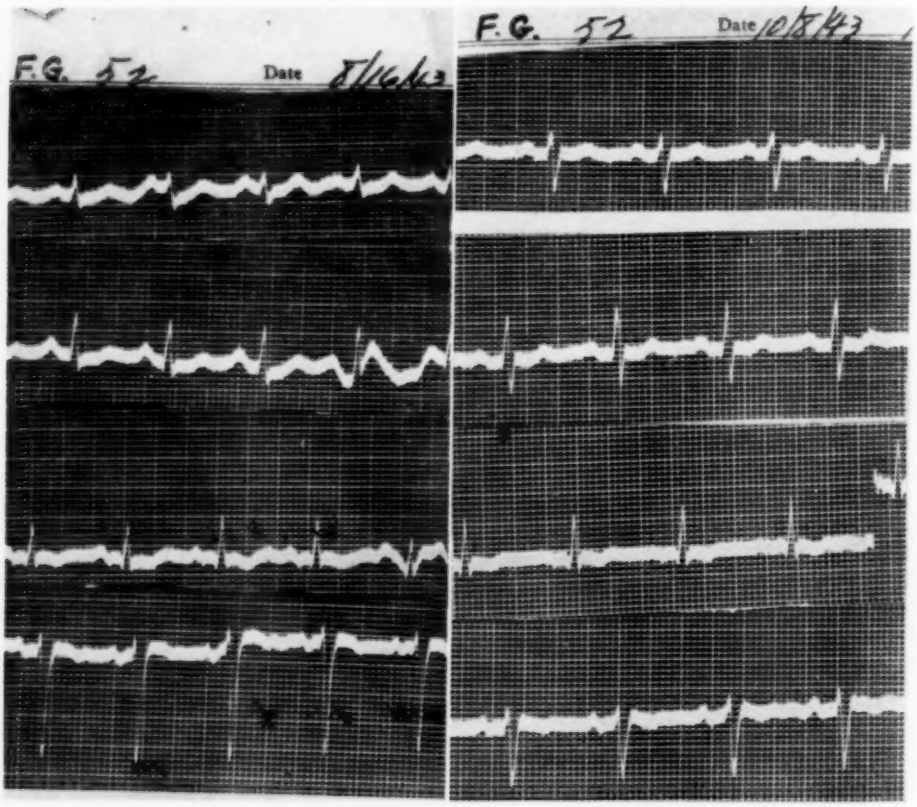
The roentgenograms and electrocardiograms indicated the presence of a cor pulmonale.

On August 14, 1943, the patient was admitted to the Multnomah Hospital with signs of advanced right-sided heart failure. A loud systolic murmur was heard all over the left second and third intercostal spaces. A short soft aortic diastolic murmur

was heard along the left margin of the sternum. The pulse was of the collapsible or Corrigan type, and the blood pressure was 135 mm. Hg systolic, 35 to 0 mm. diastolic.

Despite the prolonged intensive treatment for syphilis, the blood Kolmer and Kahn reactions remained strongly positive (four plus).

Shortly after admission to the hospital, this case was reviewed at one of the regular weekly clinical conferences, at which time a diagnosis of syphilitic aneurysm of the ascending aorta was established. However, it was further suggested that due




A. B.

FIG. 3. *A*. Electrocardiogram taken August 16, 1943, showing right axis deviation and right ventricular strain. *B*. Electrocardiogram taken October 8, 1943, indicating progressively increasing right axis deviation and right ventricular strain.

to clinical, radiologic and electrocardiographic evidence of cor pulmonale, compression of the pulmonary artery with or without perforation was probably present.

There was little response to the routine measures for congestive heart failure and the progress was continually downward. There was no significant change in the character of the murmur. The signs of congestive heart failure, chiefly right-sided, progressively increased and the patient died on January 16, 1944.

*Autopsy Findings.* The body was that of a well-developed, moderately well-nourished white male who appeared the stated age of 53 years. The external examination revealed moderate edema of the lower extremities, the scrotum, prepuce, and the posterior dependent parts of the body. No appreciable palpebral edema was seen.

The most important visceral changes were found in the ascending aorta, the pulmonary artery and the heart. About 200 c.c. of pale yellow, serous fluid were present in the pericardial sac. The heart was greatly enlarged, having a maximum transverse diameter of 17 cm. The increased size of the heart was due primarily to the right ventricular and arterial dilatation. There was moderate hypertrophy of the right ventricular myocardium. There was mild hypertrophy of the left ventricular myocardium, but this chamber was not appreciably dilated. There was no evidence of recent infarction or of myofibrosis. There was spherical aneurysmal dilatation of

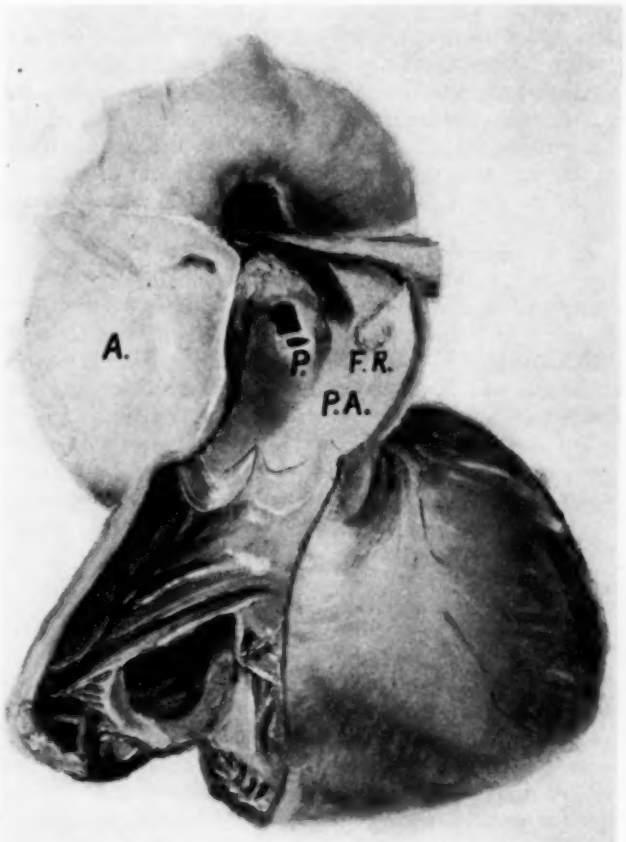



FIG. 4. Sketch illustrating the site of the aortic aneurysm at *A*, the bulge and perforations into the pulmonary artery at *P*, the widening of the pulmonary artery at *PA*, and the ring of fibrin at *FR*.

the ascending aorta. It had a diameter of 7.5 cm. The right border of the aneurysm was only slightly to the right of the usual position of the ascending aorta. The left border of the aneurysm, however, bulged to the left, pressing against and flattening the displaced main pulmonary artery. The circumference of the pulmonary artery was increased proximal to the bulge. There were two closely approximated openings into the pulmonary artery from the aortic aneurysm. The largest perforation measured 1 by 1 cm. and had the shape of a square with rounded corners. The lower border of the perforation was 3 cm. above the aortic valve commissures. Immediately below the larger opening was a smaller one which measured 6 by 3 mm. Its shape resembled

a small buttonhole. The borders of both openings were smooth and covered by intima. In the left lateral wall of the pulmonary artery opposite the perforations in the aortic wall there was a slightly raised ring of reddish, friable tissue, apparently fibrin. The ring was 1 cm. in diameter. There was no destruction of the pulmonary arterial wall.

The wall of the aneurysm of the ascending aorta was very rigid. There was such a marked amount of atherosclerosis with calcium salt deposition that the intima and subintima resembled an irregularly surfaced egg-shell. On the right lateral and anterior surfaces the aortic adventitia was thickened and there were old fibrous adhesions between the parietal pericardium and the aorta. There were irregular, plaque-like elevations of the pulmonary arterial wall above the openings from the aorta. The intima of the pulmonary artery was not roughened. The plaque-like elevations appeared to be due to irregularities in the closely approximated wall of the aortic aneurysm. A similar change was seen in the left border of the superior vena cava, where the aneurysm bulged against it. In the posterior and left lateral borders of the aneurysm the wall was very thin and seemed devoid of media. The media of the anterior and right lateral borders of the ascending aorta, however, was of the usual thickness.

The aortic valve cusps were only slightly altered. The border of the anterior cusp was slightly "rolled" and thickened. The commissure between the anterior and left posterior cusps was separated by a distance of 1 mm. The corpora Arantii and the commissures were in the same plane. The ostia of the coronary arteries also were about in this same plane. The only change in the coronary arteries was a mild atherosclerosis. There was also moderate atherosclerosis of the descending aorta. The mitral, tricuspid, and pulmonary valves were grossly unchanged.

The 800 c.c. of serous fluid in the peritoneal cavity contained some fibrin clots. A mild edema was present in the small bowel mesentery, the perirenal fat, and the mucosa and submucosa of the gastrointestinal tract. Numerous small hemorrhages were seen in the gastric mucosa and submucosa. The rounded anterior-inferior liver border was 7 cm. from the tip of the xiphoid process. The liver was mottled and had a "nutmeg" appearance. The spleen was hyperemic and slightly enlarged. The mobility of the right kidney seemed increased. In its middle portion there was a depressed area of fibrosis and cyst formation. All the cysts were less than 1 cm. in diameter; some contained a colloid-like material.

The diaphragmatic domes were depressed to the level of the sixth and seventh ribs on the right and left sides respectively. The lungs floated in 1,000 c.c. of serous fluid which were present in both pleural cavities. The visceral pleural surfaces were wrinkled and both lungs were partially atelectatic. There was no evidence of pneumonia or pulmonary infarction. All the other structures and viscera not mentioned above (with the exception of the brain, spinal cord and neck organs, which were not examined) were unchanged.

*Anatomic Diagnosis.* Syphilitic aortitis with aneurysm of the ascending aorta and erosions through the pulmonary artery; dilatation of the pulmonary artery; slight separation of an aortic valve commissure; left ventricular hypertrophy; right ventricular hypertrophy and dilatation; chronic passive congestion of the lungs; bilateral hydrothorax; bilateral pulmonary atelectasis; ascites, chronic passive congestion of the liver and spleen; retroperitoneal edema; focal fibrosis of the right kidney.

The microscopic sections confirmed the above anatomical diagnosis. In addition, the aneurysmal wall disclosed old scars of the media with occasional areas of plasma cell and lymphocytic infiltration. In association with the fibrous adventitial thickening and the pericardial adhesions, there were groups of mononuclear leukocytes and thickened arterioles. The lungs revealed the presence of edema fluid and greatly dilated capillaries of the alveolar walls. There were also focal areas of fibrosis in the alveolar walls.

## Comment

A study of the cases in the literature including the present observation suggests that compression of the pulmonary artery may be diagnosed when signs of syphilitic aortic aneurysm are associated with evidence of cor pulmonale. Pronounced hypertrophy and dilatation of the right side of the heart were present in all cases examined at autopsy. Clinically, such right-sided preponderance is less readily demonstrable; however, it may be recognized in most instances by (1) the character of venous engorgement which is largely peripheral or systemic, (2) the radiographic evidence of enlargement of the pulmonary artery and conus, and (3) electrocardiographic evidence of right-sided strain (right axis deviation, tall spiked P-waves in second and third leads, and T-wave alterations, especially in third and fourth leads).

When all these signs are present the diagnosis is relatively simple. However, recognition of pulmonary artery involvement becomes much more difficult when radiographic enlargement of the pulmonary conus is obscured by the shadow of the aneurysm and when the electrocardiogram fails to show specific changes. Significant right axis deviation was present in five of the nine cases in which tracings were available. Nevertheless, *when severe right-sided heart failure (systemic venous engorgement) supervenes in a case of syphilitic aortic aneurysm without any other discernible complication to account for the congestive failure, pulmonary artery compression should be suspected.*

In 84 of the 87 reported cases the aneurysm ruptured into the pulmonary artery and established an arterio-arterial communication; in three cases death occurred from cor pulmonale without rupture. The specific clinical sign indicating arterio-arterial communication is the development of a continuous murmur similar in character to that frequently observed in patent ductus Botalli. It is heard best over the pulmonary valve area and is often accompanied by a thrill. This sign was noted in about 40 per cent of the cases in which murmurs were described. However, even in the absence of such a murmur, arterio-arterial communication may be assumed to be present in view of the great frequency with which it was found at autopsy in the reported cases (84 out of 87).

## Summary

1. A case of compression of the pulmonary artery by a syphilitic aneurysm with arterio-arterial communication recognized during life is reported.

2. It is suggested that an antemortem diagnosis may be made more frequently through the recognition of two possible sets of symptoms or signs, one or both of which may be present in a given case:

*A.* A combination of signs of aortic aneurysm with clinical evidence of cor pulmonale.

*B.* The presence of a continuous, machinery-type murmur in the pulmonary valve area similar to that characterizing patent ductus Botalli.

## BIBLIOGRAPHY

1. Garvin, Curtis F., and Siegel, Mortimer L.: Cor pulmonale due to obstruction of the pulmonary artery by syphilitic aortic aneurysms, Am. Jr. Med. Sci., 1939, cxcviii, 679–685.

2. White, Paul D., Chamberlain, Francis L., and Kelson, Saul R.: Rupture of aorta into the pulmonary artery with long survival, Ann. Int. Med., 1941, xv, 589–597.
3. Porter, William B.: The syndrome of rupture of an aortic aneurysm into the pulmonary artery, Am. Heart Jr., 1942, xxiii, 468–482.
4. Schattenberg, Herbert J., and Harris, William H., Jr.: Aortic aneurysm with rupture into the pulmonary artery, Am. Heart Jr., 1943, xxv, 512–521.
5. Nicholson, Richard E.: Syndrome of rupture of aortic aneurysm into the pulmonary artery: review of the literature with report of two cases, Ann. Int. Med., 1943, xix, 286–325.

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## PAROXYSMAL VENTRICULAR TACHYCARDIA OCCURRING IN THE ABSENCE OF DEMONSTRABLE HEART DISEASE *

By Bernard I. Lidman, Major, M.C., A.U.S., F.A.C.P., and James M. Lyerly, Captain, M.C., A.U.S.

This case report of ventricular tachycardia is presented because of its occurrence in the presence of an apparently normal heart and as an example of the gratifying response to quinidine sulfate therapy.

Ventricular tachycardia [1, 5, 8] is indicative of the existence of serious disease, although in rare instances no cardiac pathologic lesions may be present. Among those factors thought capable of precipitating its onset are: organic heart disease, digitalis intoxication, excessive indulgence in tobacco and alcohol, marked exertion, and overwhelming fatigue.

Ventricular fibrillation [1, 4, 5, 8] has long been regarded as being a terminal state, incompatible with life if effective ventricular action is not restored rapidly. It is rarely encountered clinically, and then usually in moribund patients. High grade auriculoventricular block, acute coronary artery occlusion, chloroform anesthesia, and electrocution have resulted in ventricular fibrillation.[1, 5] In small experimental animals, application of electric shock directly to the heart may cause this irregularity, from which recovery has occurred in some instances. Overdosage with quinidine, digitalis, and epinephrine may give rise to ventricular fibrillation. This is particularly true in the case of epinephrine, when administered in the presence of a damaged, irritable myocardium.

The case to be reported is unusual because ventricular tachycardia and transient ventricular fibrillation occurred in a patient whose heart was apparently normal.

### Case Report

*Present Illness.* This white male patient, 21 years of age, was admitted to this hospital at 5:10 a.m., May 15, 1944, with the complaint of having been awakened from his sleep at 3:30 a.m. by awareness of a very rapid, irregular heart action. At the onset, he noted marked dyspnea and weakness, but stated that he had no precordial pain although his heart did feel "heavy." He had had a light dinner the previous evening, had used no alcohol or tobacco, and had not engaged in exercise preceding this attack.

*Family History.* Non-contributory. One nephew had had one mild attack of rheumatic fever.

* Received for publication February 7, 1945.

*Past History.* For one month, at the age of nine, the patient had growing pains in both legs. There was no recurrence. At the age of 15 (1938), while playing basketball, he was forced to rest because he experienced the sudden onset of rapid heart action and shortness of breath; the attack lasted three minutes. Two similar episodes occurred later under like circumstances. There was no restriction of activity by his physician. In February, 1943, he contracted pneumonia, type undetermined, and received sulfonamide therapy. During convalescence, two attacks of pharyngitis were treated with sulfonamides. On March 15, 1943, shortly after becoming ambulatory, he experienced a sudden attack of tachycardia, during which he was admitted to a hospital. On admission, the heart rate was approximately 150, and the rhythm totally irregular. An electrocardiogram, after his rhythm had become regular, showed no abnormalities except for a simple tachycardia. No electrocardiogram was taken dur-

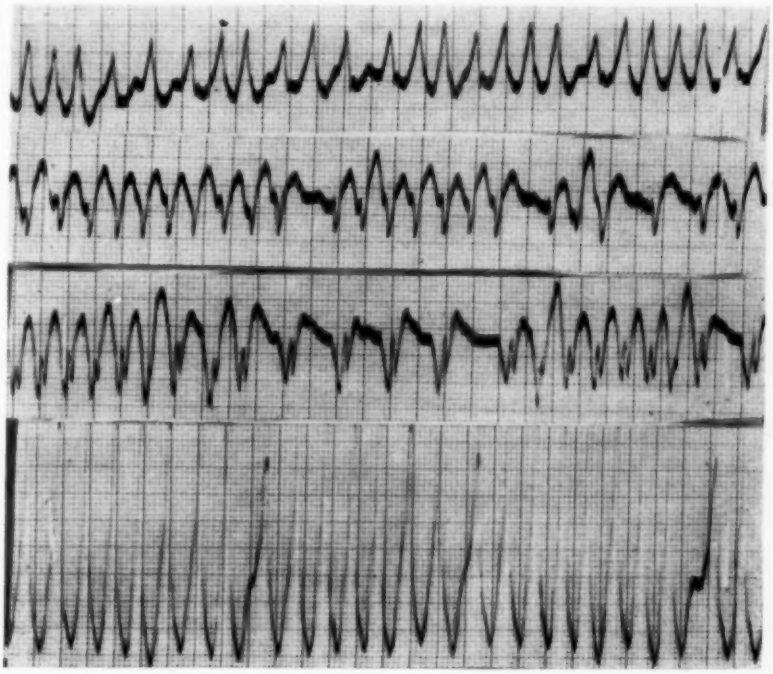


FIG. 1. 6:00 a.m., May 15, 1944.

ing the period of disturbance of cardiac rhythm. He was discharged from the hospital on March 26, 1943, with the diagnosis of paroxysmal auricular fibrillation.

After entering the armed forces, he engaged in the full physical training program without difficulty. He was not aware of any palpitation or tachycardia until the onset of the present illness.

Review of the systems was non-contributory. The patient did not use alcohol, tobacco, or drugs. He did not take any medicine habitually. There was no history of venereal disease.

No evidence of cardiac disease had been discovered during numerous examinations both prior and subsequent to the episode herein described. He had always been an emotionally stable individual.

*Physical Examination.* At the time of admission, 5:10 a.m., the patient had a

slate-gray pallor, but no cyanosis. Marked dyspnea and tachypnea were evident. The pulmonary fields showed no abnormal physical signs. The cervical veins were distended, but there was no hepatomegaly or dependent edema. The heart was not enlarged; the rate was over 200; the rhythm, grossly irregular; there was a pulse deficit of approximately 50. No murmur or friction rub was audible. Blood pressure was 90 mm. Hg systolic and 50 mm. diastolic.

*Course in Hospital.* Morphine sulfate 0.016 gm. was administered immediately, and at 6:00 a.m., an electrocardiogram was made (figure 1). At 7:15 a.m., the cardiac rate could not be counted because of extreme tachycardia; the rhythm was totally irregular. Blood pressure was 96 mm. Hg systolic and 30 mm. diastolic. Because the electrocardiogram was interpreted as showing prefibrillatory ventricular tachy-

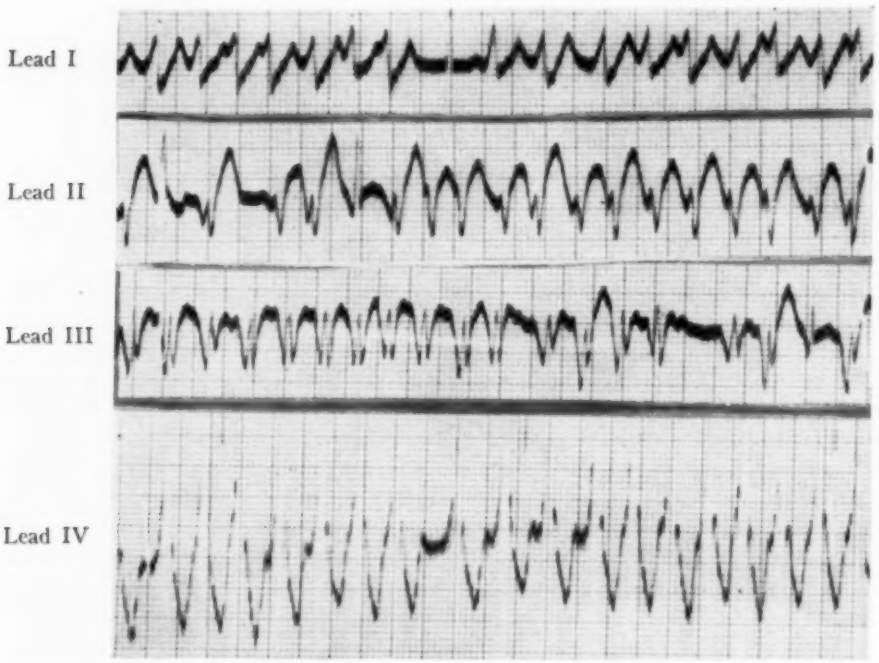


FIG. 2. 10:00 a.m., May 15, 1944.

cardia, or ventricular tachycardia with fibrillation, 1.0 gm. of quinidine sulfate was given at 8:05 a.m. At 9:30, the rate still could not be counted, but periods of regular rhythm became manifest. Blood pressure was 90 mm. Hg systolic and 50 mm. diastolic. At this time, the patient was given an additional 0.3 gm. of quinidine sulfate. An electrocardiographic tracing made at 10:00 a.m. demonstrated persistence of the arrhythmia (figure 2). At 10:45 a.m., an occasional group of heart sounds in regular rhythm was noted, and with the blood pressure at 85 mm. Hg systolic and 40 mm. diastolic, another 0.3 gm. of quinidine was administered.

At 11:00 a.m., 15 minutes after the last dose of quinidine, and following a total dosage of 1.6 gm., normal rhythm suddenly was reëstablished, at a rate of 86 beats a minute. Immediately after restoration of regular sinus rhythm (figure 3), the heart sounds were of good quality and intensity, no murmurs were audible, and the blood pressure rose to 104 mm. Hg systolic and 70 mm. diastolic.

The patient was maintained on a dosage of 0.2 gm. of quinidine sulfate every four hours for nine days. On May 24, the dose was reduced to 0.1 gm. three times daily. During this period, the blood pressure had remained at a level of 104–118 mm. systolic, and 70 mm. diastolic. The heart rate averaged 80 to 90. On only one occasion, June 3, 1944, did one examiner note a soft systolic murmur localized to the fourth left interspace. At no other time was a murmur audible.

On June 7, 1944, at 8:00 p.m., the patient had an attack of paroxysmal auricular tachycardia, with a cardiac rate of 170. He was given pantopon 0.02 gm. and quinidine sulfate 0.4 gm.; by the following morning, regular sinus rhythm had again been established.

On June 29, 1944, with the patient in an ambulatory state, he experienced an episode of supraventricular tachycardia, with rate of 260, which responded to opiates and a temporary increase in quinidine dosage.

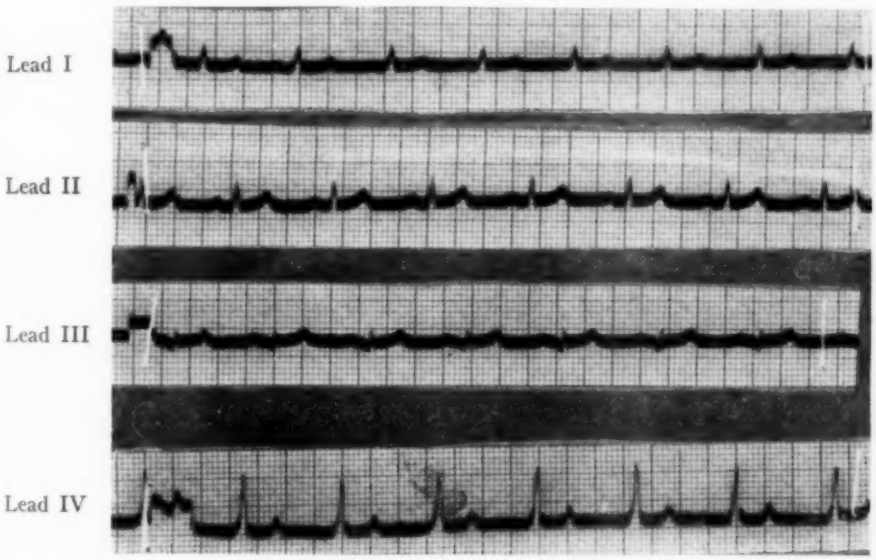


FIG. 3. 11:00 a.m., May 15, 1944.

At no time during the period of hospitalization did this patient have a leukocytosis. Erythrocyte sedimentation rates were at all times within normal limits. Serologic reaction was negative. All blood chemistry studies, including non-protein nitrogen, urea N, sugar, chlorides, cholesterol, calcium, phosphorus, and serum proteins, were normal. Basal metabolic rate was — 15 per cent. Radiographic examination revealed the heart to be normal in size and contour.

This patient was reëxamined at frequent intervals, and at no time was evidence of underlying cardiac disease discovered. The last study prior to this report was made on November 11, 1944.

*Electrocardiographic Studies.* Figures 1 and 2: These tracings were made at the height of the paroxysm, and fulfill the criteria for the diagnosis of ventricular tachycardia.[1, 3, 4, 5, 7] The main deflections are ventricular in type, widened, and notched, and occur independently of the superimposed P-waves. The complexes are unidirectional; and vary in rate from 225 to 285 with an average of 260. In figure 1, Lead III, the first six complexes are of one type, and complexes 10 to 14 in this lead

are of another type, with transitional forms between them. It might be said that each series is an arrhythmia arising in a different focus. The rate is much more rapid than that usually seen in paroxysmal ventricular tachycardia. These records might be referred to as a prefibrillatory type of ventricular tachycardia; however, they strongly resemble records of paroxysmal ventricular fibrillation overlying an impure ventricular tachycardia.

Figure 3: This record was made immediately after restoration of normal rhythm. The QRS complexes appear to be of low voltage, but standardizing deflections indicate 0.5 cm. for 1 mv., so that the QRS amplitude is within normal limits. There is no evidence of auriculoventricular block.

Serial electrocardiographic tracings made after this attack indicate no evidence of myocardial damage.

## Discussion

As previously stated, it is generally believed that ventricular tachycardia rarely if ever occurs except as a result of cardiac disease, and is of grave prognostic significance, as it may predispose to ventricular fibrillation.

In the case presented, except for growing pains at the age of nine years, there is nothing which might suggest an antecedent history of cardiac disease. The attacks of palpitation which occurred at the age of 15 were exertional in type, and no evidence of heart disease was discovered at that time. In 1943, a period of arrhythmia occurred during the patient's convalescence from an acute infection. In the present attack, no predisposing factor could be determined; and following the episode of arrhythmia, no evidence of organic cardiac disease could be discovered. Repeated sedimentation rates, leukocyte counts, serial electrocardiograms, and physical examinations did not reveal evidence of coronary artery disease, rheumatic heart disease, thyrotoxicosis, or heart block. There were no manifestations of inflammatory or circulatory change in the myocardium. The patient had undergone several physical examinations for flying qualification and never had the question of heart disease arisen.

Ventricular fibrillation, the most serious of all arrhythmias, is usually considered to be incompatible with life. However, paroxysmal ventricular fibrillation does occur, although usually in patients who have a high-grade auriculoventricular block,[6] and then may be the cause of Stokes-Adams attacks. In such instances, with the ventricular output minimal, cerebral anoxemia results.[2]

Just as some cases of paroxysmal auricular tachycardia and auricular fibrillation occur without demonstrable organic disease, paroxysmal ventricular tachycardia of the prefibrillatory type and ventricular fibrillation may exist as purely functional disturbances with no demonstrable anatomicopathological substratum.[5]

In view of the fact that previous episodes of palpitation were of short duration and ceased spontaneously, with no definitive diagnosis established by clinical or electrocardiographic study, it cannot be assumed those episodes were ventricular tachycardia. Because the attack as described herein was the most severe and of the longest duration experienced by the patient, and because there was no response to morphine sulfate within two hours of its administration, it is conceivable that quinidine sulfate played a distinct, and probably a specific rôle in the reëstablishment of normal rhythm within two hours and 40 minutes after the initial dose, and after a total dosage of 1.6 gm.

SUMMARY

A case of an unusual arrhythmia, consisting in paroxysmal prefibrillatory ventricular tachycardia, with overlying transient ventricular fibrillation, occurring in a young individual, with no demonstrable evidence of heart disease, is presented.

BIBLIOGRAPHY

1. BELLET, SAMUEL, and MCMILLAN, THOMAS M.: Diagnosis and treatment of cardiovascular disease, 1940, F. A. Davis Co., Philadelphia, pp. 656, 658.
2. FISHBERG, ARTHUR M.: Heart failure, 1937, Lea and Febiger, Philadelphia, p. 272.
3. GRAYBIEL, ASHTON, and WHITE, PAUL D.: Electrocardiography in practice, 1941, W. B. Saunders Company, Philadelphia, p. 58.
4. PARDEE, HAROLD E. B.: Clinical aspects of the electrocardiogram, 1941, Paul B. Hoeber, Inc., New York, pp. 215, 228, 243.
5. RAISBECK, MILTON C.: Personal communication.
6. SCHWARTZ and JEZER: Cited by reference 2.
7. WHITE, PAUL D.: Personal communication.
8. WHITE, PAUL D.: Heart disease, 1941, The Macmillan Co., New York, pp. 624, 659.

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## ELECTROCARDIOGRAPHIC CHANGES FOLLOWING HEAT STROKE; REPORT OF A CASE *

By ROBERT BRUCE LOGUE, Major, M.C., F.A.C.P., and JAMES FLETCHER HANSON, Major, M.C., F.A.C.P.

CARDIAC involvement in heat stroke is generally recognized. One frequently finds marked dilatation of the right ventricle with intense pulmonary congestion at autopsy. At other times the ventricles are firmly contracted in systole. Wilson [1] reported subendocardial hemorrhage in the septal region of the left ventricle in four cases. Motta [2] exposed rabbits to wet and dry heat and was able to produce a variety of cardiac conditions, such as sinus tachycardia, nodal rhythm, ventricular extrasystoles, paroxysmal auricular tachycardia, auricular flutter, auricular and ventricular fibrillation, 2 to 1 heart block, $Q_1$ and T-wave changes and increased auriculoventricular and intraventricular conduction time.

Metz [3] reported three cases with electrocardiographic changes which included bundle branch block in one case, inverted $T_1$ in one case, and posterior myocardial infarction in one case. The latter changes were probably coincidental. The rarity of reports on electrocardiographic changes in heat stroke prompts the present case report.

### CASE REPORT

A white private, aged 27, was admitted to the Station Hospital on June 3, 1943. He had been playing volley ball on a hot day and several hours later was found in his

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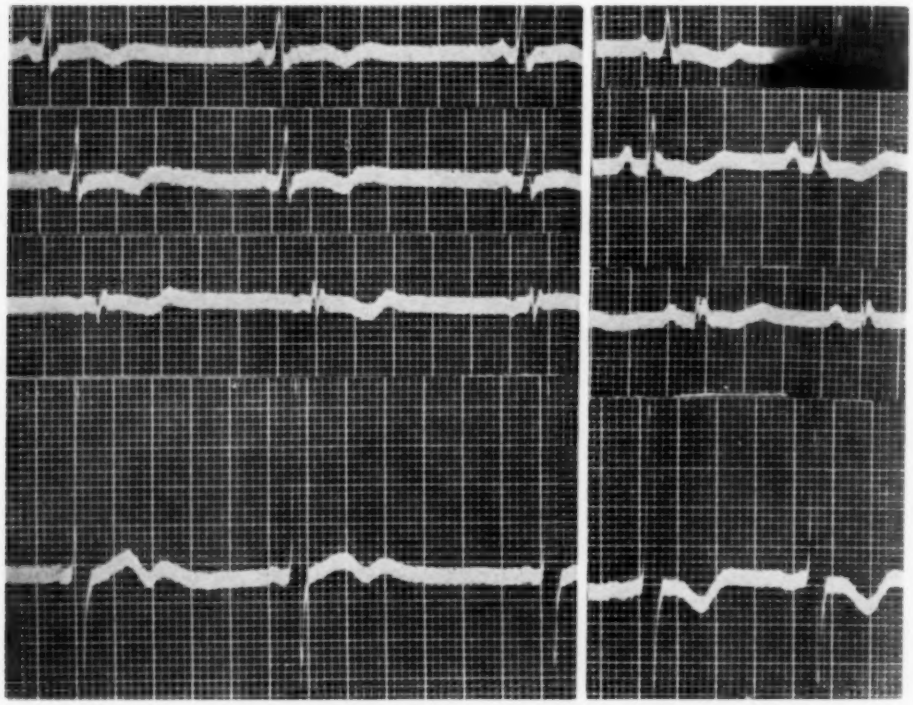
From the Cardiovascular Section, Medical Service, Lawson General Hospital, Atlanta, Georgia.

room in an unconscious state. He was irrational and was giving drill orders. Physical examination showed the patient to be extremely restless and agitated. The skin was hot, dry, and slightly cyanotic. The temperature was recorded as 109° F. The pupils were constricted and did not react. The pulse rate could not be counted accurately, but was thought to be 140 a minute. The blood pressure could not be obtained. The examination of the heart showed it to be of normal size. No murmurs were heard. Laboratory data on admission showed a red blood cell count of 4.3 million. The hemoglobin was 95 per cent (Tallquist). A white blood cell count was 11,700. Urinalysis showed a specific gravity of 1.016, 3 plus albumin, occasional



A B

FIG. 1. Electrocardiogram (A) on eleventh and (B) on twenty-first hospital days.

hyaline and granular casts, and 2 to 4 red blood cells and 1 to 2 white blood cells in each high power field.

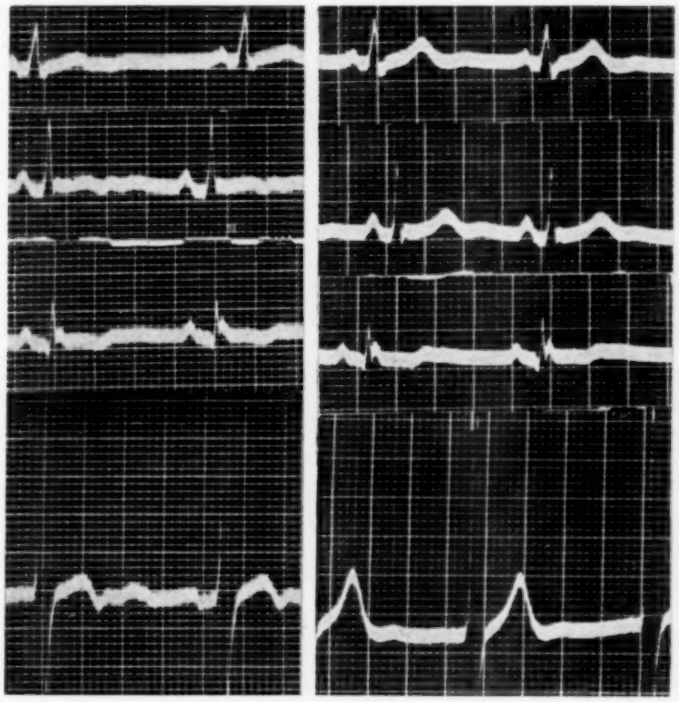
The patient was sprayed and massaged, and four hours later the temperature had fallen to 105° F. The next morning the temperature was 102.6° F. At this time the patient was incontinent and mentally confused, but could answer questions. The pulse was thought to show an occasional irregularity. He was given 1500 c.c. of plasma and six ampules of digiglusin intramuscularly over a period of 24 hours. On the third hospital day the patient was noted to be jaundiced. The red blood cell count was 4.3 million, and the hemoglobin was 75 per cent. The white blood cell count was 3,900. Other laboratory data at this time revealed a bleeding time of 12 minutes, a clotting time of five minutes, and a platelet count of 91,600. The total protein content of the blood plasma was 6.4 gm., with 4 gm. of albumin and 2.4 gm. of globulin. The

cephalin-cholesterol flocculation test was 3 plus. The icterus index was 57. Subsequently the patient developed ascites, a palpable liver and spleen, and albuminuria, with many red and white blood cells in the urine. The icterus index gradually returned to normal over a period of one month.

On the eleventh hospital day an electrocardiogram showed sinus bradycardia, inversion of the T-waves in all leads, and prominent U-waves (figure 1-A).

On the twelfth hospital day the cephalin cholesterol flocculation test was 2 plus, and on the seventeenth hospital day it was 1 plus.

On the twenty-first hospital day there was deeper inversion of the T-waves in Lead IV (figure 1-B). Two months after the original electrocardiogram, the tracing



A B

FIG. 2. Electrocardiogram after (A) two months and (B) three months.

showed slight inversion of $T_1$ and diphasic $T_2$ and inverted $T_3$ and $T_4$ (figure 2-A). Three months after the original electrocardiogram the tracing had returned to normal, but U-waves were still present (figure 2-B).

During convalescence the patient complained of nervousness and a slight tremor of the hands. These had been present for some years but were exaggerated following the heat stroke. An occasional low grade fever, reaching as high as 99.6° was noted.

A psychiatric consultant made a diagnosis of psychoneurosis with anxiety state. An electroencephalogram taken on July 27, 1943 showed "an underlying encephalopathy revealed by almost complete absence of the basic rhythm and a markedly increased fast rhythm." A repeat record taken three months later showed a normal borderline tracing. There was evidence of gradual brain recovery, and a distinct re-

turn towards normal with increase in amplitude and the appearance of the basic rhythm with 10 waves a second; continued intermittent appearance of low amplitude waves of 6 a second, and some increase beyond normal of the fast waves to 20 to 25 a second.

## Comment

The presence of jaundice is of some interest and may have been due to direct action on the liver by the hyperpyrexia, to the administration of plasma, or it may have been coincidentally present. The sudden appearance and rapid subsidence suggest that it was a toxic effect of the hyperpyrexia. Jaundice has been reported incident to artificial fever therapy, as well as to natural exposure.[4] The occurrence of anemia, plus evidence of renal damage, might suggest a hemolytic reaction, although ascites is not usually seen in this condition.

The nature of the electrocardiographic changes is somewhat confusing, since the patient had been in profound shock and a digitalis preparation had been administered for 24 hours. Digitalis may cause inversion of the T-waves in all leads; however, the absence of depressed or sagging ST segments, the normal PR interval, and time required for the changes to disappear made this unlikely. Inversion of the T-waves in all leads may be seen following extremely rapid rates,[5] but this was not felt to be a factor in the present case. The pulse rate as recorded on admission was admittedly inaccurate, but was thought to be about 140. Subsequent pulse recordings in the first 24 hours were rapid, but not excessively so.

The changes noted are similar to those seen in pericarditis. The elevation of the ST segments which is usually seen in the early stages of this condition, is not present; however, the first tracing was not taken until the eleventh hospital day. In view of the reports of hemorrhage into the septum, subendocardial hemorrhage, and hemorrhage beneath the pericardium [6] observed at autopsy following sunstroke, it is possible that the changes were perhaps associated with subepicardial hemorrhage or pericardial hemorrhage. Hemorrhagic manifestations are not uncommon in heat stroke, and it is evident that diffuse capillary damage is a not infrequent occurrence. The bradycardia was perhaps a vagal effect of central origin, and is of some interest in view of the electroencephalographic changes suggestive of encephalopathy. The sinus bradycardia disappeared after two months, and a repeat electroencephalogram made one month later showed a return to normal.

## Summary

A case of heat stroke, in which the electrocardiographic changes observed were suggestive of those seen in pericarditis, is reported. The changes were associated with sinus bradycardia and gradually disappeared over a period of two and one-half months.

## BIBLIOGRAPHY

1. Wilson, Gale: The cardiopathology of heat stroke, Jr. Am. Med. Assoc., 1940, cxiv, 557.
2. Motta, Giovanni: Il comportamente dell' elettrocardiogramma del colpo de calore provocato sul coniglio, Riv. d. pat. sper., 1937, vii, 141.
3. Metz, E.: Herzschädigung durch Hitzschlag im Elektrokardiogram, Klin. Wchnschr., 1940, xix, n. r. xi, 247.

4. SAFFERT, CORNELIUS: Heat hyperpyrexia, Minnesota Med., 1937, xx, 106.
5. GEIGER, ARTHUR: Electrocardiograms simulating those of coronary thrombosis after cessation of paroxysmal tachycardia, Am. Heart Jr., 1943, xxvi, 553.
6. SMITH, EBEN E.: Heat stroke a thermoregulatory incompetency, U. S. Nav. Med. Bull., 1928, xxvi, 479.
7. MARSH, FRANK: Heat stroke and heat exhaustion, Brit. Encyclopaedia of Medical Practice, Butterworth & Co., Ltd., London, 1937.

# EDITORIAL

## *THE Rh FACTOR*

SINCE the practical significance of the Rh agglutinogen and its corresponding agglutinin was shown by Wiener and Peters [1] in 1940, a great deal of intensive study has been devoted to this subject. This has revealed many facts of great theoretical interest and of practical importance. The subject has become so intricate, however, and the diversity in nomenclature so confusing that recent publications are apt to bewilder the average reader who has no first hand acquaintance with this work. The earliest work on this subject was reviewed briefly in these pages.[2] Some of the subsequent developments will be summarized but, for the sake of clarity and simplicity, shorn of much detail. Wiener, Levine, Race, Taylor and their associates have contributed largely to this work.

As a rule, any individual is compatible as a donor if he belongs to the same major blood group as the recipient. In rare instances, however, individuals who had received repeated transfusions of homologous blood eventually developed a severe hemolytic reaction even though in some cases the same donor had been used previously without causing any reaction. A careful study of the blood in three such cases [1] revealed the presence in the recipients' serum of agglutinin which caused clumping of the donor's cells. This was due to the presence of an agglutinable substance in the donor's cells which is different from the agglutinogens A and B which determine the major blood groups. The new agglutinogen was designated Rh, because the corresponding agglutinin was identical with one which Landsteiner and Wiener had produced in rabbits by inoculations of blood from rhesus monkeys.

By means of such human sera as well as serum from "immunized" animals they demonstrated that this Rh factor (agglutinogen) was present in the red cells of 85 per cent of random white individuals. In the 15 per cent of Rh-negative persons anti-Rh agglutinins ordinarily are not demonstrable. They may appear, however, after sensitization by repeated transfusions of Rh-positive blood. They may also appear, independent of transfusions, in women who are pregnant with an Rh-positive fetus, particularly in cases of erythroblastosis fetalis. Such women may give a hemolytic reaction to the first transfusion of Rh-positive blood. It is believed that fetal red blood cells enter the maternal circulation, presumably through defects in the placenta, and stimulate the development of anti-Rh agglutinin. Conversely, the agglutinin may pass from the maternal into the fetal circulation and

[1] WIENER, A. S., and PETERS, H. R.: Hemolytic reactions following transfusions of blood of homologous group, with 3 cases in which same agglutinogen was responsible, Ann. Int. Med., 1940, xiii, 2306–2322.

[2] Editorial: The significance of human atypical isoagglutinins, Ann. Int. Med., 1941, xv, 927–929.

injure the red blood cells, causing the anemia. The antigenic activity of the Rh factor, however, seems to be relatively feeble, since agglutinins appear in only about 2 to 4 per cent of the cases in which they might be expected.

The Rh factor is not a single simple substance. Further study showed that different human anti-Rh agglutinating sera differ qualitatively in their action on different Rh-positive cells. Three specific varieties of anti-Rh agglutinating sera have been described: (1) the standard anti-Rh serum (since designated as anti-$Rh_0$ agglutinin by Wiener), which agglutinates the red cells of 85 per cent of white individuals; (2) a second type, anti-Rh′, which agglutinates the cells of 70 per cent; and (3) a type, anti-Rh″, which agglutinates only 30 per cent. There are about 2 per cent of individuals who are Rh-positive but not revealed by the first type of serum. Sera occur which contain two of these agglutinins, e.g. anti-$Rh_0$ and anti-Rh′, and anti-$Rh_0$ and anti-Rh″.

Those red cells which are Rh-positive contain agglutinable factors corresponding to these three agglutinins, which Wiener has termed $Rh_0$, Rh′, and Rh″. These factors occur, either singly or in combination, to form at least five (probably seven) different agglutinogens or antigens. Wiener [3] has designated these as Rh′, Rh″, $Rh_0$, $Rh_1$ (= $Rh_0'$), and $Rh_2$ (= $Rh_0''$). The British investigators have postulated the existence of two additional antigens, $Rh_y$ (= Rh′″) and $Rh_z$ (= $Rh_0'''$), both very rare, of which only the latter has been demonstrated.

These agglutinogens are inherited as dominant Mendelian characters, through pairs of allelic genes, one from each parent. There are five (possibly seven) such genes corresponding to the agglutinogens listed, designated *Rh′*, etc., and a sixth, *rh*, a recessive character which, when homozygous, determines an Rh-negative individual.

By means of the three varieties of anti-Rh agglutinating sera it is possible to divide all human beings into eight Rh Types or 'groups.' The designations and frequency of these Types in the white population are given by Wiener [3] as follows: $Rh_1$ $Rh_2$, 13 per cent; $Rh_1$, 54.5 per cent; $Rh_2$, 15 per cent; $Rh_0$, 2 per cent; Rh′ Rh″, 0.01 per cent; Rh′, 1.2 per cent; Rh″, 0.3 per cent; and Rh-negative, 13.5 per cent. The relative frequency of the types varies in other races. In Mongolians Rh-negative individuals are extremely rare.

A study of mothers with infants with erythroblastosis has shown that in about 92 per cent of the cases the mother is Rh-negative, whereas the fetus is Rh-positive, having inherited the Rh factor from the father. In 8 per cent, however, the mother is Rh-positive, and some other type of incompatibility must be concerned. Levine [4] reported finding agglutinins in the serum of such a case, which acted on an agglutinable factor in the fetal

[3] Wiener, A. S.: The Rh blood factors, Jr. Am. Med. Assoc., 1945, cxxvii, 294. (Correspondence.)

[4] Levine, P., Burnham, L., Katzin, E. M., and Vogel, P.: Rôle of iso-immunization in pathogenesis of erythroblastosis fetalis, Am. Jr. Obst. and Gynec., 1941, xlii, 925–937.

red cells which was analogous to but different from the Rh factor. He termed this the Hr factor, because the corresponding anti-Hr agglutinin in its activity was just the reciprocal of the anti-Rh′ agglutinin. This serum agglutinated the bloods of 80 per cent of white individuals including all those who are Rh-negative. This observation was confirmed and extended by Race and Taylor [5] who advanced the theory (which is accepted by Wiener) that the 'Hr factor' is determined in the cells (of the fetus) by certain of the Rh factors: viz., rh, $Rh_0$, Rh″ and $Rh_2$. If these factors are absent from the mother (who must possess other Rh factors, $Rh_1$ or Rh′, since she is "Rh-positive"), she may become sensitized to them just as if she were completely Rh-negative.

The Hr factor seems to be only feebly antigenic, since this relationship has been found in less than 3 per cent of the cases of erythroblastosis. Theoretically an Hr-negative recipient might be sensitized by repeated injections of Hr-positive blood, but no report of such a case has been found. The British investigators postulate the existence of two other Hr factors and anti-Hr agglutinins reciprocal in their action to anti-$Rh_0$ and anti-Rh″ agglutinin. One case of the latter type has been described.

There is no universally accepted explanation as to why erythroblastosis rarely if ever occurs as a result of incompatibility between mother and fetus with respect to the major isoagglutinogens A and B; e.g., when a mother belongs to Group O, and the fetus to A or B. In a majority of individuals in the latter groups, however, the group substance, A or B, is present not only in the red cells but also in the plasma, the cells of many other tissues and in the secretions. Such cases are called secretors. It has been suggested that the group substance (A or B) which is in the plasma or elsewhere combines with any anti-A or anti-B agglutinin that may pass from the maternal into the fetal circulation and thus prevents its reaching and injuring the red cells. The Rh factor seems to be limited to the red cells and not present in the other tissues or secretions.

As might be expected there are still differences of opinion regarding the explanation of these complicated relationships. Bloods are occasionally encountered which do not fit perfectly into this scheme. The discrepancy may be in the agglutinability of the red cells or in the agglutinative activity of the serum. There is some evidence that other varieties of specific agglutinating serum occur which may define additional Rh Types.[6] There is one discrepancy which warrants brief mention. Although in about 90 per cent of the cases of erythroblastosis the mother is Rh-negative, in a substantial number of the latter the serum shows no anti-Rh agglutinating activity. It was shown independently by Wiener and by Race [7] that if Rh-

[5] Race, R. R., and Taylor, G. L.: Serum that discloses genotype of Rh-positive people, Nature, 1943, clii, 300.

Race, R. R., Taylor, G. L., Cappell, D. F., and McFarlane, M. N.: Recognition of further common Rh genotype in man, Nature, 1944, cliii, 52.

[6] Levine, P.: On the Hr factor and the Rh genetic theory, Science, 1945, cii, 1–4.

[7] Race, R. R.: Incomplete antibody in human serum, Nature, 1944, cliii, 771–772.

positive cells are added to such serum, in many cases the cells lose their agglutinability in other potent anti-Rh serum. Wiener attributed this inhibition of agglutination to "blocking" antibodies, Race to "coating" or "incomplete" antibodies, in the sense that although they combine with the Rh factor in the cells and prevent potent agglutinin from acting later, they are unable to bring about the actual clumping. The demonstration of such specific inhibition of agglutination may probably be regarded as proof that the individual was sensitized.

One may now well ask, what is the practical significance of all this complicated business. As far as the subdivision of the Rh factor into types is concerned, there are as yet few opportunities to utilize this practically. Their determination may be useful for medicolegal purposes, e.g. in excluding paternity, along with a study of the other isoagglutinogens. If the necessary sera are available, and some of them are very rare indeed, in the case of the father of an infant with erythroblastosis it may be possible in certain cases to determine his genotype,[5] and predict whether all or only half of his future children are likely to have the disease. Such matters are only for the specialist.

In certain cases, however, in selecting donors for transfusion it is of great practical importance to know whether the recipient and donor are Rh-positive or negative. For this purpose the usual anti-Rh serum suffices, since only 0.5 to 2 per cent of Rh-positive bloods will be missed. For the average laboratory, there are practical difficulties in finding and preparing suitable sera. The most dependable sera are obtained from mothers of infants with erythroblastosis. Except in large clinics such cases are relatively rare, and in only a part of these cases do the mothers yield serum which has a sufficiently high agglutinin titer to be dependable for diagnostic purposes. Such sera tend to weaken rapidly, both in vitro and in vivo, and may become useless within a few weeks. Furthermore anti-A or anti-B agglutinin must be removed by adding specific A and B substance. This may be prepared from the saliva of secretors. Fortunately for laboratories unable to cope with these difficulties, it is now possible to purchase reliable standard anti-Rh serum which is ready for use.

The tests are best carried out in small test tubes, rather than in hanging drops, and the results observed both macroscopically and microscopically. Incubation should be in the water bath at 37° C., since a large majority of the sera are most active at that temperature. In rare cases, however, agglutination is stronger in the ice box. The technic of performing the tests is not complicated or difficult. At best, however, the agglutinations produced by these sera are usually feeble as compared with those observed in ordinary group determinations, and correspondingly greater care is required to obtain reliable results.

The most practicable way of making this information available to all who need it is probably by establishing special Rh-typing laboratories in connection with state or city Health Departments, as has recently been done

in Baltimore by the Obstetrical and Gynecological Section of the Baltimore City Medical Society.

In summary, tests for the Rh factor should be carried out: (1) on all individuals receiving repeated transfusions; (2) on women pregnant or recently pregnant, regardless of previous transfusions; and (3) on a sufficiently large number of normal individuals to provide a working list of Rh-negative donors available for emergencies. If the prospective recipient is Rh-negative, it is highly advisable to secure an Rh-negative donor. A transfusion, if badly needed, should not ordinarily be withheld on this account, since the chance of a severe reaction is less than 1 in 25. An Rh-negative donor is imperative, however, for a patient who tends to react increasingly to repeated transfusions, and for mothers of infants with erythroblastosis. If an infant with erythroblastosis is to be transfused, the mother should never be used as a donor.[8] Almost anyone else may ordinarily be used provided they are compatible with respect to the major blood groups. It is probably advisable, however, to avoid using as donors those who have themselves received transfusions of blood or injections of plasma.

[8] Washed red cells from the mother may be used.

# REVIEWS

*Recent Advances in Neurology and Neuropsychiatry.* By W. Russell Brain, M.A., D.M. (Oxon.), F.R.C.P., and E. B. Strauss, M.A., D.M. (Oxon.), F.R.C.P. 363 pages; 21 × 14 cm. 1945. The Blakiston Company, Philadelphia. Price, $5.00.

This book in its fifth edition needs little more to be said about it than has been said before. In its previous editions it has been considered a good guide to the subject with clear and comprehensive discussions of the various viewpoints. As always there is a full bibliography for each topic for the use of those who want more detailed information. In addition to being full of well selected facts it is well written and easily read. Although the title includes neuropsychiatry the emphasis throughout is almost entirely on neurology and even the few more psychiatrically pointed chapters deal with the subject matter from a neurological rather than a functional viewpoint.

The first part of the book deals with headaches and intracranial disease. The recent work with histamine in the production of headaches and the rationale for the use of ergotamine tartrate in migraine is touched upon. This leads to a discussion of the use and value of various diagnostic methods in cases of suspected intracranial disease. Meningitis in its various forms, with the emphasis on head symptoms, brings in the uses of the newer drugs of the sulpha group and penicillin. What can and cannot be expected of these drugs is well illustrated.

The next section deals with the more nearly neuropsychiatric problems. Electro-encephalography, prefrontal leukotomy and electro-convulsant therapy are given a thorough discussion. The uses and abuses of all three are thoroughly evaluated. The authors feel that electro-encephalography has made great stride but also realize its limitations in diagnosis if used without other diagnostic procedures. They are fair to the enthusiasts about prefrontal leukotomy but feel it is a procedure to be tried only after careful consideration and after efforts to treat in less drastic methods have failed. Head injuries, their diagnosis, prognosis and treatment are discussed in this section also and some of the things that have been helpful in treating them which have been learned through these other procedures. Electroconvulsant therapy is described in great detail and with enthusiasm. The authors feel it is indicated particularly in the affective psychoses, but cite cases where it has been used with some benefit in almost any psychotic or even psychoneurotic condition. The pathology and symptomatology of Alzeimer's and Pick's diseases are described and the differential diagnosis is made to appear much simpler than it actually is in most cases.

After this excursion into neuropsychiatry the book comes back to more purely neurological subjects, the anatomy and functions of the hypothalamus, the neuro-physiology of micturition and defecation, the neurotropic viruses and the diseases they cause. These topics are all interestingly discussed and the newer concepts emphasized. There is a good description of much of the research in the physiology and anatomy of the functions of micturition and defecation.

The rest of the book takes up briefly the topics of vitamins and their rôle in neurology and neuropsychiatry, the peripheral nerves, their regeneration and degeneration after injury, the muscular diseases, sciatica and the current enthusiasm for operation in its treatment and an interesting type of shoulder girdle neuritis. In discussing all of these things the newer research and the old concepts are given a fair description with the authors taking a rather conservative attitude but ready to give the new treatment and theories a trial.

Altogether this is a factual, unbiased book covering the field of neurology, and

touching its relationship to neuropsychiatry (more actually in the foreword than in the text), which anyone interested in the field of neurology or psychiatry or, indeed, general medicine will find a convenient reference work for looking up a subject briefly or for finding in it a reference to more detailed work.

R. K. G.

*Case Studies in the Psychopathology of Crime.* By BEN KARPMAN, M.D. 738 pages; 21 × 28 cm. Medical Science Press, Washington, D. C. 1944. Price, $10.00.

This is the second volume in a series of three, reporting a study on the psychopathology of crime. The first volume was published in 1933 and was reviewed in this journal. The third volume is yet to come off the press. The author is a psychoanalyst, and a Senior Medical Officer at St. Elizabeth's Hospital, Washington, D. C., the Federal hospital for the insane. He has had unlimited opportunity to study psychopathic criminals committed from the Federal Prisons.

In the first volume Karpman presented a detailed study of five cases. In this volume he presents the psychoanalysis of four cases, but without his psychoanalytic interpretation. The material is presented without expurgation and the reader has no difficulty in recognizing the psychological mechanisms involved. In the first volume the cases were studied psychogenetically rather than psychoanalytically. The four cases presented in this volume were charged with sexual crimes and the reader cannot miss the etiological factors underlying this type of misbehavior. The anamnesis is clearly presented and one concludes that if the individuals had been properly handled in childhood, they would not have set off on their careers of crime. There is no doubt that crime prevention begins in infancy and childhood, rather than adulthood.

The tabulation of criminal behavior, conduct in prisons, and drug addiction is well worth reading and is accurate for detail.

This ponderous volume is certainly not for the lay reader, but for the physician interested in social problems, it is an excellent source for case study and may well act as a model for thoroughness and exactness.

J. L. McC.

## BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

*A Synopsis of the Diagnosis of the Surgical Diseases of the Abdomen.* Second Edition. By JOHN A. HARDY, B.Sc., M.D., F.A.C.S. 528 pages; 20 × 13 cm. 1945. C. V. Mosby Company, St. Louis. Price, $5.00.

*In the Doctor's Office.* By ESTHER JANE PARSONS. 295 pages; 19.5 × 13.5 cm. 1945. J. B. Lippincott Company, Philadelphia. Price, $2.00.

*Modern Urology for Nurses.* By SHEILA MAUREEN DWYER, R.N., B.S., and GEORGE W. FISH, M.D. With a foreword by Helen Young, R.N. 287 pages; 20.5 × 14 cm. 1945. Lea & Febiger, Philadelphia. Price, $3.25.

*Prescribing Occupational Therapy.* Second Edition. By WILLIAM RUSH DUNTON, JR., M.D. 151 pages; 22.5 × 14.5 cm. 1945. Charles C. Thomas, Springfield, Illinois. Price, $2.50.

*War Neuroses.* By ROY R. GRINKER, Lt. Col., M.C., and JOHN P. SPIEGEL, Major, M.C., Army Air Forces. 145 pages; 23.5 × 16 cm. 1945. The Blakiston Company, Philadelphia. Price, $2.75.

*Penicillin in the Treatment of Infections.* By CHESTER S. KEEFER, B.S., M.S., M.D., ScD. (Hon.), and DONALD G. ANDERSON, A.B., M.D. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), F.A.C.P., Hon. F.R.C.P. (Can.). Reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work. 51 pages; 24 × 16 cm. 1945. Oxford University Press, New York. Price, $1.50.

*Hematology for Students and Practitioners.* By WILLIS M. FOWLER, A.B., M.D., with a chapter by ELMER L. DEGOWIN, A.B., M.D. 499 pages; 24 × 16.5 cm. 1945. Paul B. Hoeber, Inc., New York. Price, $8.00.

*Guia de Trabajos Practicos (Serie Aromática).* 225 pages; 27.5 × 19 cm. 1945. Universidad Nacional de Tucuman. Facultad de Farmacia y Bioquimica. Catedra de Quimica Organica Ciclica.—Publicacion No. 372. Tucuman, República Argentina.

# COLLEGE NEWS NOTES

## A.C.P. Members in the Armed Forces

### *Additions*

At the time of the release of this news item, the following 52 additional Fellows and Associates of the American College of Physicians, recently elected, have been added to the list of members on active military duty during World War II, making a grand total of 1,980:

Leonard Max Asher, Los Angeles, Calif. (Major, MC, AUS)
Oscar Auerbach, Staten Island, N. Y. (Lieutenant, MC, USNR)
Noyes Latham Avery, Jr., Ann Arbor, Mich. (Major, MC, AUS)
Arthur Dwight Baldwin, Wellesley, Mass. (Captain, MC, AUS)
Malcolm Lynn Barnes, Louisville, Ky. (Captain, MC, AUS)
William Edwin Barnett, Logansport, Ind. (Major, MC, AUS)
Ward Wright Briggs, Wilmington, Del. (Lieutenant Commander, MC, USNR)
Norman Quintus Brill, New York, N. Y. (Lieutenant Colonel, MC, AUS)
Heinrich Georg Brugsch, Boston, Mass. (Lieutenant, MC, AUS)
Thomas Edison Clark, Columbus, Ohio (Lieutenant, MC, USNR)
Wilfrid Joseph Comeau, Bangor, Maine (Lieutenant Colonel, MC, AUS)
William Dean Coventry, Duluth, Minn. (Major, MC, AUS)
Arthur Charles Darrow, St. Louis, Mo. (Major, MC, AUS)
Nicholas John Di Gregorio, Brooklyn, N. Y. (Major, MC, AUS)
Henry Dunlop Ecker, (Passed Assistant Surgeon, USPHS)
Robert William Elliott, St. Louis, Mo. (Major, MC, AUS)
Roberto Francisco Escamillo, San Francisco, Calif. (Major, MC, AUS)
Walter Goldfarb, New York, N. Y. (Major, MC, AUS)
Robert Philip Harvey, Denver, Colo. (Major, MC, AUS)
Thomas Gideon Hobbs, Chicago, Ill. (Major, MC, AUS)
Milton E. Hubbard, Los Angeles, Calif. (Lieutenant Colonel, MC, AUS)
Lewis Edward January, Iowa City, Iowa (Major, MC, AUS)
William Allen Jeffers, Philadelphia, Pa. (Major, MC, AUS)
Milosh Kasich, Weehawken, N. J. (Lieutenant Colonel, MC, AUS)
Robert Willis Kimbro, Cleburne, Tex. (Captain, MC, AUS)
Gerald Klatskin, New Haven, Conn. (Major, MC, AUS)
J. Elliot Levi, Baltimore, Md. (Captain, MC, AUS)
Isaiah Edward Libin, New York, N. Y. (Captain, MC, AUS)
Joseph Francis Linsman (Colonel, MC, USA)
Mischa J. Lustok, Milwaukee, Wis. (Lieutenant Colonel, MC, AUS)
Harold Aloysius Lyons (Lieutenant Commander, MC, USN)
Lumir Martin Mares, Wenatchee, Wash. (Major, MC, AUS)
Harold Henry Marquis, San Francisco, Calif. (Major, MC, AUS)
Theodore H. Mendell, Philadelphia, Pa. (Lieutenant Colonel, MC, AUS)
Louis Merves, Philadelphia, Pa. (Captain, MC, AUS)
Richard Marion Nay, Rochester, Minn. (Lieutenant, MC, AUS)
Leslie Staebler Pierce, Greensburg, Pa. (Major, MC, AUS)
Leon Rosove, Santa Monica, Calif. (Lieutenant Commander, MC, USNR)
John Jerome Rupp, Santa Barbara, Calif. (Commander, MC, USNR)
Robert Bruce Rutherford, Peoria, Ill. (Colonel, MC, AUS)
John Paul Sauvageot, Akron, Ohio (Captain, MC, AUS)
Ralph Kenneth Shields, Bethlehem, Pa. (Captain, MC, AUS)

Norman Richard Shulack, Brooklyn, N. Y. (Major, MC, AUS)
Leslie Benjamin Smith, Phoenix, Ariz. (Lieutenant Colonel, MC, AUS)
Spicknall, Charles Gassaway (Surgeon, USPHS)
Irwin Daniel Stein, Mt. Vernon, N. Y. (Captain, MC, AUS)
Robert Harold Talkov, Boston, Mass. (Captain, MC, AUS)
Leonard Tarr, New York, N. Y. (Major, MC, AUS)
Paul Luke White, Austin, Tex. (Major, MC, AUS)
Donald Eugene Wood, Indianapolis, Ind. (Major, MC, AUS)
Donovan George Wright (Lieutenant Commander, MC, USN)
Thomas Ziskin, Minneapolis, Minn. (Major, MC, AUS)

The following members of the College have recently been separated from active duty:

James P. Baker, Richmond, Va. (Lt. Col., MC, AUS)
L. Minor Blackford, Atlanta, Ga. (Major, MC, AUS)
Oscar Blitz, New Orleans, La. (Col., MC, AUS), (Associate)
Joseph G. Bohorfoush, Madison, Wis. (Major, MC, AUS)
William J. Bondurant, Jr., San Antonio, Tex. (Lt. Col., MC, AUS)
George A. Boylston, Wilmette, Ill. (Major, MC, AUS), (Associate)
J. Russell Brink, Grand Rapids, Mich. (Lt. Comdr., MC, USNR), (Associate)
Daniel Noyes Brown, Westport, Conn. (Capt., MC, AUS)
Morton Goodwin Brown, Boston, Mass. (Lt. Col., MC, AUS), (Associate)
Benjamin Burbank, Brooklyn, N. Y. (Major, MC, AUS)
Hildahl Ingbert Burtness, Santa Barbara, Calif. (Comdr., MC, USNR)
Roy Edwin Butler, New Orleans, La. (Senior Surgeon, USPHS)
Asher Spafford Chapman, Oyster Bay, N. Y. (Capt., MC, AUS), (Associate)
David Hale Clement, Buffalo, N. Y. (Capt., MC, AUS)
Stuart R. Combs, Terre Haute, Ind. (Capt., MC, AUS), (Associate)
Joseph Russell Cook, Huntington, W. Va. (Major, MC, AUS), (Associate)
Crispin Cooke, New York, N. Y. (Capt., MC, AUS), (Associate)
Dolph Lange Curb, Houston, Tex. (Lt. Col., MC, AUS)
Hal Davis, Roanoke, Va. (Capt., MC, AUS), (Associate)
Norman Walter Drey, St. Louis, Mo. (Lt. Col., MC, AUS), (Associate)
J. Richard Durham, Wilmington, Del. (Major, MC, AUS)
Eli Eichelberger, York, Pa. (Capt., MC, AUS), (Associate)
David E. Engle, Elmhurst, Ill. (Major, MC, AUS), (Associate)
Irving Ershler, Binghamton, N. Y. (Major, MC, AUS)
William Dustin Evans, Los Angeles, Calif. (Major, MC, AUS), (Associate)
Edwin G. Faber, Tyler, Tex. (Col., MC, AUS)
Isidore Albert Feder, Brooklyn, N. Y. (Lt. Col., MC, AUS)
James Owen Finney, Gadsden, Ala. (Major, MC, AUS)
Dan W. Fisher, Lansing, Mich. (Lt. Col., MC, AUS), (Associate)
Arthur Conwell Fortney, Fargo, N. D. (Major, MC, AUS)
Carl H. Fortune, Lexington, Ky. (Lt. Col., MC, AUS)
Dale G. Friend, Boston, Mass. (Col., MC, AUS)
Victor K. Funk, Oak Terrace, Minn. (Comdr., MC, USNR)
Clark C. Goss, Seattle, Wash. (Capt., MC, USNR)
George C. Griffith, Philadelphia, Pa. (Lt. Comdr., MC, USNR)
Lawrence J. Halpin, Cedar Rapids, Iowa (Major, AUS), (Associate)
Samuel Hantman, Cleveland, Ohio (Major, MC, AUS), (Associate)
Carl A. Hartung, Chattanooga, Tenn. (Major, MC, AUS)
Theodore S. Heineken, Bloomfield, N. J. (Major, MC, AUS), (Associate)
Ferdinand C. Helwig, Kansas City, Mo. (Lt. Col., MC, AUS)

Joe E. Holoubek, New Orleans, La. (Major, MC, AUS), (Associate)
Ralph C. Hoyt, Reading, Pa. (Major, MC, AUS)
Robert R. Janjigian, Forty Fort, Pa. (Lt. Col., MC, AUS)
William Karl Keller, Louisville, Ky. (Lt. Comdr., MC, USNR)
LeMoyne Copeland Kelly, New York, N. Y. (Comdr., MC, USNR)
Roy E. Kinsey, Peekskill, N. Y. (Major, MC, AUS), (Associate)
Jack D. Kirshbaum, Chicago, Ill. (Lt. Col., MC, AUS)
Jacob Joseph Kirshner, Philadelphia, Pa. (Lt. Col., MC, AUS), (Associate)
Andrew J. V. Klein, East Orange, N. J. (Capt., MC, AUS)
James Edward Knighton, Jr., Shreveport, La. (Lt. Col., MC, AUS)
Rudolph A. Kocher, Carmel, Calif. (Lt. Col., MC, AUS), (Associate)
Alfred L. Kruger, Jersey City, N. J. (Capt., MC, AUS), (Associate)
Edward R. H. Kurz, Brooklyn, N. Y. (Major, MC, AUS)
Louis H. Landay, Pittsburgh, Pa. (Lt. Col., MC, AUS)
William A. Lange, Brooklyn, N. Y. (Lt. Col., MC, AUS)
Sidney Leibowitz, New York, N. Y. (Lt. Col., MC, AUS), (Associate)
Joseph Levy, New Rochelle, N. Y. (Capt., MC, AUS), (Associate)
Max August Lindauer, Philadelphia, Pa. (Capt., MC, AUS), (Associate)
Louis S. Lipschutz, Eloise, Mich. (Lt. Col., MC, AUS), (Associate)
Victor Wesley Logan, New York, N. Y. (Capt., MC, USNR)
Hugh MacDonald, Glenview, Ill. (Lt. Col., MC, AUS), (Associate)
Dean W. Marquis, East Orange, N. J. (Comdr., MC, USNR)
George Elmer Martin, Pittsburgh, Pa. (Lt. Col., MC, AUS), (Associate)
George Graydon Martin, Buffalo, N. Y. (Comdr., MC, USNR)
Edward Matzger, San Francisco, Calif. (Lt. Comdr., MC, USNR), (Associate)
Charles K. Maytum, Rochester, Minn. (Col., MC, AUS)
Jesse McCall, Newton, N. J. (Lt. Col., MC, AUS)
Ernest G. McEwen, Evanston, Ill. (Major, MC, AUS)
John McDowell McKinney, New York, N. Y. (Lt. Comdr., MC, USNR)
John R. E. Morgan, Toronto, Ont. (Lt. Col., RCAMC)
Samuel Nesbitt, New Haven, Conn. (Lt., MC, USNR)
George Francis O'Brien, Chicago, Ill. (Lt. Col., MC, AUS)
Sidney G. Page, Jr., Richmond, Va. (Major, MC, AUS), (Associate)
Harold W. Palmer, Wichita, Kans. (Major, MC, AUS)
Elmus D. Peasley, Raleigh, N. C. (Major, MC, AUS), (Associate)
Paul August Petree, Harrisburg, Pa. (Lt. Col., MC, AUS), (Associate)
Morton Morris Pinckney, Richmond, Va. (Major, MC, AUS), (Associate)
Norman Plummer, New York, N. Y. (Major, MC, AUS)
L. Paul Ralph, Grand Rapids, Mich. (Comdr., MC, USNR), (Associate)
William A. Read, Cleveland, Ohio (Lt. Col., MC, AUS), (Associate)
W. Grady Reddick, Dallas, Tex. (Lt. Comdr., MC, USNR)
Samuel T. R. Revell, Jr., Baltimore, Md. (Capt., MC, AUS), (Associate)
Harold F. Robertson, Philadelphia, Pa. (Lt. Col., MC, AUS)
Max Harry Rosenblum, Steubenville, Ohio (Major, MC, AUS), (Associate)
Owen Royce, Jr., Oklahoma City, Okla. (Major, MC, AUS), (Associate)
John W. Skinner, Kirkland, Wash. (Capt., MC, USNR)
Joseph Sklaver, Waterbury, Conn. (Capt., MC, AUS), (Associate)
Carter Smith, Atlanta, Ga. (Lt. Col., MC, AUS)
Walter M. Solomon, Cleveland, Ohio (Lt. Col., MC, AUS)
James Ward Sours, Peoria, Ill. (Lt. Comdr., MC, USNR)
Alfred Stengel, Jr., Philadelphia, Pa. (Capt., MC, AUS)
Franz H. Stewart, Miami, Fla. (Lt. Comdr., MC, USNR)
Dar Delos Stofer, Monterey, Calif. (Capt., MC, USNR)
James M. Strang, Pittsburgh, Pa. (Lt. Col., MC, AUS)

Paul Richard Swanson, Chattanooga, Tenn. (Capt., MC, AUS), (Associate)
James Shirley Sweeney, Dallas, Tex. (Col., MC, AUS)
Charles F. Sweigert, San Francisco, Calif. (Lt. Col., MC, AUS), (Associate)
James M. Suter, Bristol, Va. (Major, MC, AUS), (Associate)
William A. Thornhill, Jr., Charleston, W. Va. (Lt. Comdr., MC, USNR), (Associate)
R. Carmichael Tilghman, Baltimore, Md. (Lt. Col., MC, AUS)
J. Russell Twiss, New York, N. Y. (Capt., MC, USNR)
Gilman R. Tyler, Richmond, Va. (Major, MC, AUS), (Associate)
William Clifford Vance, Richmond, Ind. (Capt., MC, AUS), (Associate)
Arie C. van Ravenswaay, Boonville, Mo. (Lt. Col., MC, AUS), (Associate)
Aloysius Vass, Springfield, Ill. (Capt., MC, AUS)
John Orren Vaughn, Santa Monica, Calif. (Comdr., MC, USNR), (Associate)
Joseph James Wallace, Washington, D. C. (Major, MC, AUS), (Associate)
Arthur Brittan Walter, Saint John, N. B., Can. (Col., RCAMC)
Joseph O. Weilbaecher, Jr., New Orleans, La. (Lt. Col., MC, AUS)
Thomas J. White, Jersey City, N. J. (Lt. Col., MC, AUS)
Hugh Grigsby Whitehead, Jr., Baltimore, Md. (Comdr., MC, USNR)
M. Richard Whitehill, Norfolk, Va. (Major, MC, AUS), (Associate)
Russell D. Williams, Monterey, Calif. (Major, MC, AUS), (Associate)
Sidney E. Wolpaw, Cleveland, Ohio (Major, MC, AUS)

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### A.C.P. Governors Return from Military Service

During the period of the war several members of the Board of Governors of the College have served on active military duty. During their absence Acting Governors were appointed who served meritoriously. With the end of the war the following Governors have now returned and have resumed their active work, relieving the Acting Governors:

Dr. Edward L. Bortz, Philadelphia, Governor for Eastern Pennsylvania, relieving Dr. Thomas M. McMillan, Philadelphia, Acting Governor.

Dr. Douglas Donald, Detroit, Governor for Michigan relieving Dr. Patrick L. Ledwidge, Detroit, Acting Governor.

Dr. Charles E. Watts, Seattle, Governor for Washington, relieving Dr. Edwin G. Bannick, Seattle, Acting Governor.

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### 27th Annual Session of the College, Philadelphia, Pa., May 13–17, 1946

As announced in the December issue of this journal, the 27th Annual Session of The American College of Physicians will be held in Philadelphia, Pa., May 13–17, inclusive, 1946, under the general chairmanship of Dr. George Morris Piersol, 36th and Spruce Streets, Philadelphia 4, Pa. Dr. Piersol is organizing all local arrangements, the program of Morning Clinics, Panel Discussions and entertainment features. Working with him are the following chairmen of local committees: Dr. Edward L. Bortz, Entertainment Committee; Dr. Harrison F. Flippin, Committee on Transportation; Dr. Thomas Fitz-Hugh, Committee on Clinics; Mrs. William D. Stroud, Committee on Ladies' Entertainment.

The President of the College, Dr. Ernest E. Irons, 122 S. Michigan Avenue, Chicago 3, Illinois, is organizing the program of Morning Lectures and Afternoon Scientific Sessions. Many of the speakers and subjects have already been decided upon, but additional titles may be submitted directly to Dr. Irons.

The Executive Secretary, Mr. E. R. Loveland, is responsible for all business arrangements, and for the Technical Exhibit. Some three thousand rooms have been reserved in advance at Philadelphia hotels. The Benjamin Franklin Hotel, 9th and Chestnut Streets, will be general hotel headquarters for Officers, Regents and

Governors, and for such additional members as can be accommodated. A list of hotels and their rates will be published shortly. The Municipal Auditorium, 34th Street below Spruce, will be the headquarters for the Morning Lectures, Panel Discussions, Afternoon Scientific Sessions, Committee Meetings and the Technical Exhibit. It is anticipated that the finest and largest Technical Exhibit ever conducted by the College will be arranged. The Technical Exhibit is conducted on a high plane; all exhibits irrelevant to the practice of internal medicine and its allied specialties will be eliminated. Exhibitors and exhibits will be selected with particular care from an Invitation List already prepared.

Perhaps the greatest feature of the Meeting will be the Victory Convocation on Wednesday evening, in the Grand Ballroom of the Benjamin Franklin Hotel, where Fellowships will be awarded to all physicians who have qualified for Fellowship since the outbreak of the War. An impressive ceremony has been organized, and will be under Dr. Reginald Fitz, Marshal of the College.

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### New Life Members of the College

The following Fellows have become Life Members since the publication of the last issue of this journal. They are listed in the order of subscription. The Life Membership fee is deposited in the permanent Endowment Fund of the College, and each Life Member becomes an active Fellow so long as he lives. The Life Membership fees may properly be deducted on Federal income tax returns. This means there is considerable saving on subscriptions to Life Memberships during the period when Federal taxes are high.

Dr. Seymour Harry Silvers, Brooklyn, N. Y.
Dr. Samuel Nesbitt, Arlington, Va.
Dr. Elmer Edward Glenn, Springfield, Mo.
Dr. Wilton Ross Glenney, Pottsville, Pa.
Dr. David Wendel Carter, Jr., Dallas, Texas
Dr. Irving Gray, Brooklyn, N. Y.
Dr. James Francis Slowey, Cleveland, Ohio

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The following gifts to the College Library of Publications by Members are gratefully acknowledged:

M. G. Berry, Major, (MC), AUS, Associate, San Francisco, Calif.—1 reprint.
Dr. Carlos F. Cardenas y Pupo, F.A.C.P., Havana, Cuba—5 reprints.
Samuel Hantman, Major, (MC), AUS, Associate, Greensboro, N. C.—1 reprint.
Dr. Benjamin Kaufman, Associate, Brooklyn, N. Y.—1 reprint.
Dr. Thomas H. McGavack, F.A.C.P., New York, N. Y.—3 reprints.
Milton Mendlowitz, Captain, (MC), AUS, Associate, San Francisco, Calif.—1 reprint.
Dr. Leslie M. Smith, F.A.C.P., El Paso, Tex.—2 reprints.
Dr. Robert M. Stecher, F.A.C.P., Cleveland, Ohio—1 reprint.
J. S. Sweeney, Colonel, (MC), AUS, F.A.C.P., Dallas, Tex.—1 reprint.

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At the Thirteenth Annual Assembly of The Omaha Mid-West Clinical Society, October 22–26, 1945, twenty-seven Fellows and one Associate of the College appeared on the scientific program or on committees. Of this number, the following were distinguished guests from other states:

Dr. Burrill B. Crohn, F.A.C.P., New York, N. Y., "Peptic Ulcer—A Modern Concept of a Psychosomatic Disease," "Inflammatory Diseases of the Small Intestine,"

"Clinic—Diseases of the Colon"; Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio, "The Purpuric States," "The Splenic Dyscrasias: Differential Diagnosis and Treatment," "Clinic—Differential Diagnosis and Therapeutic Rationale in Anemic States," "Round Table—Anemias Which Do not Respond to Orthodox Therapy"; Dr. Lester R. Dragstedt, F.A.C.P., Chicago, Ill., "Newer Developments in the Surgical Treatment of Gastro-duodenal Ulcer," "Surgery of the Pancreas," "Clinic—Duodenal, Gastric and Gastro-jejunal Ulcers," "Round Table—Surgery of the Gall-bladder"; Major Thomas Jan Dry, (MC), AUS, F.A.C.P., Camp Carson, Colo., "Thermal Injuries Occurring under Conditions of Combat," "Scientific Exhibit—Trench Foot and Frost Bite"; Dr. Robert H. Felix, F.A.C.P., Washington, D. C., "Maladjustment in the Returning Veteran—Comments on Etiology and Symptomatology," "Mental Public Health: A Blue Print," "Clinic—Adjustment Problems in Returning Veterans"; Dr. John A. Toomey, F.A.C.P., Cleveland, Ohio, "Respiratory Emergencies in the Infant and Child," "Differential Diagnosis of Meningeal Irritations," "Clinic—Children with Neurologic Organic Lesions," "Round Table—Treatment of Contagious Diseases."

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### The American College of Physicians Regional Meeting for North Carolina

A Regional Meeting of the College was held at Durham, N. C., November 30, 1945, under the Governorship of Dr. Paul F. Whitaker, F.A.C.P., Kinston, and a committee consisting of Dr. J. P. Rousseau, F.A.C.P., Chairman, Winston-Salem, Dr. E. R. Hedgpeth, F.A.C.P., Chapel Hill, Dr. E. S. Orgain, F.A.C.P., Durham, Dr. F. R. Taylor, F.A.C.P., High Point. The Scientific Program, conducted at Duke Hospital, was as follows:

1. The Nutritional State of the Civilian Population of Southern Germany.
   Julian M. Ruffin, M.D., F.A.C.P., Durham.
2. Blood Coagulation and Modern Clinical Applications.
   John H. Ferguson, M.D., F.A.C.P., Chapel Hill.
3. The Surgical Treatment of Hypertension.
   Keith S. Grimson, M.D., (by invitation).
4. Subacute Bacterial Endocarditis.
   Robert L. McMillan, M.D., (associate), Winston-Salem.
5. The Management of Congestive Heart Failure.
   William T. Rainey, M.D., F.A.C.P., Fayetteville.

A Dinner Meeting and Evening Session were held at the Hope Valley Country Club, at which Dr. Whitaker presided. The speaker of the evening was Dr. Frederic M. Hanes, F.A.C.P., Professor of Medicine, Duke University School of Medicine, the subject being "Ameboid Movement of Cancer Cells as a Factor in Metastasis."

A large proportion of Fellows and Associates of the College from the State of North Carolina were in attendance, and in addition there were numerous guests. The entire meeting was declared an outstanding success.

The 1946 Regional Meeting for North Carolina will be held at the Bowman Gray School of Medicine at Winston-Salem, and Dr. E. L. Persons, F.A.C.P., Durham, will be the Chairman of the Program Committee.

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### Academy-International of Medicine and Dentistry Seeks Medical Reprints for the Devastated Medical Libraries of Manila

In connection with its campaign to help rebuild the medical libraries of Manila which were destroyed during the Japanese occupation, the Academy-International of Medicine requests that medical authors contribute eight or ten reprints of each of their articles which have been published since 1941. They may be sent at the regular

parcel post rate of sixteen cents for the first pound and eleven cents for each additional pound, care of A. B. M. Sison, M.D., Philippine General Hospital, Manila, P. I.

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Dr. William W. Cadbury, F.A.C.P., has left the United States to return to Lingnan University at Canton, China. Prior to the war, Dr. Cadbury was Professor of Internal Medicine there and Superintendent of the Canton Hospital.

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The Medical Society of the State of Pennsylvania will hold its 96th Annual Session at the Bellevue-Stratford Hotel, Philadelphia, October 7–10, 1946, according to announcement by its Secretary-Treasurer, Dr. Walter F. Donaldson, F.A.C.P., Pittsburgh.

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According to a recent announcement, Tulane University of Louisiana School of Medicine, New Orleans, has been given a bequest of $1,075,000 from Miss Sarah Henderson for the endowment of the chair of tropical medicine and for the improvement and expansion of the department.

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Dr. Pascal F. Lucchesi (Associate) has recently been released as a Lieutenant Colonel from an assignment in Uruguay as Chief of a Health and Sanitation Mission for the Commission of Inter-American Affairs and has resumed his duties as Superintendent and Medical Director of the Philadelphia Hospital for Contagious Diseases.

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Under the Presidency of Dr. Oscar Swineford, Jr., F.A.C.P., Charlottesville, Virginia, the American Academy of Allergy held its second Annual Meeting at Chicago, December 10–11.

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### Major General George F. Lull Accepts Appointment with American Medical Association

Major General George F. Lull, (MC), USA, F.A.C.P., Deputy Surgeon General of the United States Army, has accepted an appointment as Assistant Secretary of the American Medical Association, and has already assumed his duties in Chicago. It was recently announced that Dr. Olin West, after a great many years of service, will retire to the status of Secretary Emeritus later in the year, and General Lull will then assume the full duties as Secretary.

General Lull was awarded the Distinguished Service Medal for "exceptionally meritorious conduct in the performance of outstanding services in the Office of The Surgeon General from June 1940 to August 1945." First commissioned into the Army Medical Reserve as a First Lieutenant in 1912, General Lull had reached the rank of temporary Lieutenant Colonel by 1918, though he later reverted to the rank of Major until the confirmation of his rank as Lieutenant Colonel in 1933. In 1939 he was promoted to Colonel, in 1943 to Brigadier General, and later in 1943 to his present rank. He served in France with the AEF as Commanding Officer of Base Hospital No. 35, and, previous to World War I, in the Canal Zone. He served in various positions at Walter Reed General Hospital, including Chief of Laboratory Service, Director of Laboratories and Professor of Bacteriology, Director of the Occupational Therapy Department, and Instructor at the Army Medical School. In addition to these duties, he has served as Assistant to the Eighth Corps Area Surgeon, Medical Advisor of the Governor General of the Philippines, and as Director of Military Personnel and Chief of the Statistical Division in the Office of the Surgeon General.

The citation: "In his capacity as Chief of the Personnel Service he was responsible for developing plans to augment the various officers' corps and the enlisted and civilian personnel of the Medical Department during the nation's first total mobilization of medical manpower. As Deputy Surgeon General, he was largely responsible

for establishing policies and directing studies which resulted in many outstanding medical achievements such as the advancement in preventive health measures, the remarkably low incidence of disease, and the low mortality from both disease and battle wounds. General Lull's skillful discharge of difficult duties and his devotion to the mission of the Medical Department contributed in important degree to the success of the Army's unprecedented medical program."

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Dr. Harold Innman Goslin, F.A.C.P., has accepted the medical directorship of the Wabash Valley Sanitarium at Lafayette, Ind. He began his duties during November.

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Dr. Theodore Rothman (Associate), Los Angeles, Calif., addressed the Los Angeles Society of Neurology and Psychiatry, November 21, 1945, on "Recent Trends in Electroencephalography."

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Dr. Willard C. Rappleye, F.A.C.P., President of the Josiah Macy, Jr. Foundation, New York City, has announced that more than five million copies of over four hundred leading medical and scientific articles have been published by the Foundation's War Reprint Service during the last three years for medical officers of the Armed Forces of the United States, and in so far as possible, Canada, England, New Zealand, Australia, the Union of Socialist Soviet Republics and China. The Reprint Service will now be discontinued because of plans for demobilization of the Armed Forces.

The Reprint Service has been an effort to bring new and important developments in the science and practice of medicine to medical officers who were largely cut off from the sources of medical information during the war. The Committee on Pathology of the National Research Council and of the National Committee for Mental Hygiene actively coöperated in the selection of these articles. The distribution of the reprints was worked out in coöperation with the Surgeons General of the Army and Navy and the Air Surgeon.

In addition to the articles reproduced from journals, the Foundation published for the Air Surgeon, five original monographs, prepared by medical officers of the Army Air Forces, dealing with personality disturbances occurring in combat zones. Over ninety-five thousand copies of these monographs were distributed as official documents of the Office of the Air Surgeon. Eight additional monographs and nine reviews of medical literature on subjects of military interest have been prepared, and seventy thousand copies distributed. Since August 1944, a News Letter for the Rheumatic Fever and Streptococcus Control Program of the Army Air Forces has been published monthly for the Air Surgeon, and over one thousand copies each month were mailed to interested medical officers, military hospitals and medical school libraries. Through the coöperation of the Interdepartmental Committee on Cultural and Scientific Coöperation of the Department of State, sixty thousand reprints have been distributed to medical teachers and investigators in forty-eight foreign countries. The Office of War Information requested permission to circulate the Foundation's reprints among more than thirty of their foreign Outposts, and has reduplicated selected articles for their distribution to medical leaders abroad.

The Foundation expended more than $225,000 in financing the War Reprint Service.

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Dr. Lester M. Morrison, F.A.C.P., has removed from Philadelphia to Los Angeles, where he has entered the practice of internal medicine at 1911 Wilshire Boulevard.

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Dr. Hyman I. Goldstein (Associate) has been appointed Professor of the History of Medicine at the Essex College of Medicine and Surgery, Newark, N. J.

Dr. Guy G. Lunsford, F.A.C.P., Atlanta, has been appointed Deputy Director of the Georgia Department of Public Health. Dr. Lunsford is a native Georgian, and received his medical education at the University of Georgia and Vanderbilt School of Public Health. He is widely known throughout Georgia, and has been director of the division of local health organizations since 1934, and prior thereto was health officer in Crisp and Jenkins counties.

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### New York University College of Medicine Announces Plans for a New Medical Center

New York University has announced plans for construction of a $27,500,000 Medical Center on the East Side, of which its share will cost $15,000,000. The project will be known as the New York University-Bellevue Medical Center and Chancellor Harry Woodburn Chase has indicated construction of the University's section would begin in a year or two. The City will spend $12,500,000 to rebuild its present Bellevue Hospital area, which will adjoin the University's new buildings along First Avenue. The combined project will cover the nine city blocks between 25th and 34th Streets, First Avenue to East River Drive.

The University section of the project will include a new College of Medicine building, a University Clinic, and 480-bed University Hospital, a 279-room Hall of Residence for medical students, a 500-seat auditorium, and an Institute of Forensic Medicine, the latter the first of its kind in the world.

Where Bellevue Hospital devotes most of its services to the very poor, the University project will concentrate on benefits to persons of moderate means. In the hospital, stress will be placed on single rooms, because the tendency is in that direction. But partitions will be removable if there is unexpected demand for ward service.

There will be six institutions housed in New York University structures. One H-shaped building to cost $8,500,000 will be 19 stories high and contain the clinic on the bottom floors, the College of Medicine above that, and superimposed on them both will be a 14-floor hospital. The Hall of Residence, to provide sleeping quarters for 270 students now living in rooming houses in the Bellevue area, will cost $750,000.

The Institute of Forensic Medicine will be built by the City on land to be provided by New York University. University faculty members will staff it. It will be the first such institution in the world, and its purpose will be to train a new type of medical examiner with a view to replacing the old coroner system in the field of criminal investigation.

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### Bureau of Medicine and Surgery Announces Program for Training of Specialists

Establishment of a long-term program for training of specialists, involving the designation of nine large naval hospitals as special centers of instruction, is announced by Vice Admiral Ross T. McIntire, U.S.N., F.A.C.P., Chief of the Bureau of Medicine and Surgery.

Intended to fulfill more adequately the medical and surgical needs of an expanded peacetime Navy, the program will make available to medical officers a complete term of specialization training comparable to the best obtainable in civil life. All of the recognized specialties will be taught, including anesthesiology, dermatology and syphilology, internal medicine, neurosurgery, obstetrics and gynecology, ophthalmology, orthopedic surgery, otolaryngology, pathology, pediatrics, plastic surgery, psychiatry and neurology, radiology, surgery and urology.

The nine postgraduate teaching centers will be set up at the following naval hospitals: Chelsea, Massachusetts; St. Albans, New York; Philadelphia, Pennsylvania;

Bethesda, Maryland; Great Lakes, Illinois; San Diego, Long Beach and Oakland, California, and Seattle, Washington.

The board of honorary consultants to the Navy Medical Department of the Navy, composed of ranking civilian members of the profession, have actively coöperated in formulation of plans and will assist in their development. The consultants are: Dr. Donald C. Balfour, director of the Mayo Foundation and Clinic, Rochester, Minnesota; Dr. Richard B. Cattell, Chief of the Surgical Section, Lahey Clinic, Boston, Massachusetts; Dr. Edwin J. Cohn, Department of Physical Chemistry, Harvard Medical School, Boston, Massachusetts; Dr. Frank P. Corrigan, American Ambassador to Venezuela; Dr. Walter E. Dandy, Professor of Neurosurgery, Johns Hopkins University Hospital, Baltimore, Maryland; Dr. Frank H. Lahey, Director of the Lahey Clinic, Boston, Massachusetts; Dr. Oswald S. Lowsley, Director of the Department of Urology, James Buchanan Brady Foundation, New York, New York; Dr. James E. Paullin, F.A.C.P., Professor of Clinical Medicine, Emory University, Atlanta, Georgia; Dr. W. Calhoun Stirling, Urologist, Washington, D. C.; Dr. Edward A. Strecker, F.A.C.P., Professor of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; Dr. Meyer Wiener, Professor of Ophthalmology, Washington University, St. Louis, Missouri.

Instructors will include not only the regular staffs of the nine special training centers but also members of the naval Reserve Medical Corps who are outstanding in their various fields of medicine and surgery. Duties of the latter, as volunteers, will include consultations in problem cases and organization of the curricula. Headquarters of the program will be in the Bureau of Medicine and Surgery, and a central advisory committee will be created.

Present plans, which are flexible, call for a definite period of training for the young doctor who enters the Navy upon his graduation from medical school. This period would cover one year's internship, one or more years of residency training, two years of sea or foreign shore duty and, finally, a definite period of intensive work in this country in that field of medicine which the officer has chosen and which has been approved by the central advisory group.

Chief advantage of the program, from the individual doctor's point of view, is that it gives him an opportunity to become a specialist without the financial, assignment and other complications which attend the same effort in civil life. The training will not be given to those medical officers who do not wish to specialize or who demonstrate that they are better fitted for general practice.

Internships and residency training will continue to be given at all naval hospitals which are properly accredited, with the more advanced teaching offered at the nine specialization centers. Augmenting the latter will be the postgraduate facilities of a number of civilian teaching institutions, to be announced later.

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### Mississippi Valley Medical Society 1946 Essay Contest

The Mississippi Valley Medical Society is resuming its annual Essay Contest in 1946, and offers a cash prize of one hundred dollars, a gold medal, and a certificate of award for the best unpublished essay on any subject of general medical interest (including medical economics) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best.

Contestants must be members of the American Medical Association and residents of the United States. The winner will be invited to present his contribution before the next Annual Meeting of the Society, to be held at St. Louis, Mo., September 25–27, 1946. The Society reserves the exclusive right to first publish the essay in its official journal. All contributions shall not exceed five thousand words, shall be typewritten in English in manuscript form, and shall be submitted in five copies not later than

May 1, 1946, to Dr. Harold Swanberg, F.A.C.P., Secretary of the Society, 209 W. C. U. Bldg., Quincy, Ill.

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### Pediatric Antiques on Tour

The Collection of Pediatric Antiques, illustrated in the pages of a catalogue just issued, has evolved into one of considerable historical importance, depicting as it does the progression of infants' feeding vessels from the Greece of twenty-five centuries ago down to the present. This Collection was started as a personal hobby of the late E. Mead Johnson, Jr., and it has been steadily growing in size and scope, and is of increasing interest for teaching purposes via the historical route. The destruction of original sources caused by the War tends to add to the value of these objects. The Collection is now available to colleges, hospitals, museums, libraries and other institutions of learning. Application for its use should be sent to the curator, Mead Johnson & Company, Evansville 21, Ind.

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Dr. Dar Delos Stofer, F.A.C.P., has retired as a Captain in the U. S. Naval Reserve, and on December 1, 1945, established private practice at 412 Professional Bldg., Monterey, Calif. Before the War Dr. Stofer was located in Kansas City, Mo.

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### American University of Beirut in Lebanon to Construct Medical Center

Plans for the construction of a Medical Center at the American University of Beirut, Lebanon, at an estimated cost of $2,500,000, have been announced by Albert W. Staub, American Director of the Near East College Association, Inc. The University's Board of Trustees has approved this project. The Medical Center will increase the bed capacity of the present hospital by more than 250 per cent, make possible the training of 25 per cent more medical students and treble the size of the Nursing School. Mr. Staub predicted that when the Center is in operation, American medicine will come into the foreground in the Near East.

The Medical Center will provide accommodations for guest research fellows in tropical medicine. Conditions in the Near East are suitable for research in malaria, typhoid fever, dysenteries and typhus, and for the investigation of nutritional diseases in children. As a teaching hospital, the building will contain classrooms in conjunction with clinical work, administrative offices, living quarters for internes, staff suites, rooms for the nursing staff and guest rooms.

The American University of Beirut, one of the eight colleges affiliated with the Near East College Association, was founded in 1866 with a charter from the State of New York. Its Medical Scholo opened a year later. The University is the largest American educational institution outside the United States.

"The Medical Center will enhance American prestige and build up friendship for the United States," Mr. Staub said. "Evidence of the prestige already attained by the American University of Beirut Hospital is the large percentage of its patients who come from countries as far distant as Iraq, Iran and Egypt. It has served members of royal families of several surrounding countries, as well as Lebanese and Syrian ministers who often are alumni of the University."

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Brigadier General William C. Menninger, F.A.C.P., Director of Neuropsychiatry Consultants Division, has been on a tour of inspection of Medical Department installations in the Pacific, including stops at Honolulu, Guam, Shanghai, Chungking, and Tokyo.

## A.C.P. Postgraduate Program for 1946

At the present writing, plans for our Postgraduate Program for 1946 are about to crystallize. Directors have authorized courses in the following subjects listed:

| *Subject* | *Location* | *Dates* | *Director* | *Institution* | *Capacity* |
|---|---|---|---|---|---|
| Allergy | Boston, Massachusetts | Mar. 4–9<br>Apr. 8–13<br>May 1 wk. | Dr. F. M. Rackemann | Massachusetts General Hospital | 6 only<br>6 only<br>6 only |
| Allergy | New York, New York | Nov. 4–16 | Dr. Robert A. Cooke | Roosevelt Hospital | 30–75 |
| Arthritis | New York, New York | Apr. 15–20 | Dr. Ralph H. Boots | Presbyterian Hospital | 10–20 |
| Cardiology | Philadelphia, Pa. | May 6–11 | Dr. W. G. Leaman, Jr. | Philadelphia General Hospital, and Woman's Medical College | 75–100 |
| Chemotherapy | St. Louis, Missouri | Oct. or Nov. 1 wk. | Dr. W. Barry Wood, Jr. | Washington University, and Barnes Hospital | 10–20 |
| Chest Diseases | Ann Arbor, Michigan | May 6–11 | Dr. John Alexander | University of Michigan | 25–75 |
| Gastroenterology | Philadelphia, Pa. | Apr. 29–May 4 | Dr. Henry L. Bockus | Graduate Hospital, and Philadelphia General Hospital | — |
| General Medicine | Atlanta, Georgia | Apr. 22–27 | Dr. James Paullin | Emory University | — |
| General Medicine | Galveston, Texas | Mar. or Apr. 1 or 2 wks. | Dr. Charles T. Stone | University of Texas | — |
| General Medicine | Philadelphia, Pa. | Mar. 18–23 | Dr. Hobart Reimann | Jefferson Hospital | 75–100 |
| Hematology | Columbus, Ohio | Oct. 21–26 | Dr. Charles A. Doan | Ohio State University | 35–75 |
| Internal Medicine | Boston, Massachusetts | Apr. 1–19 | Dr. J. H. Means | Massachusetts General Hospital | 60–80 |
| Neurology and Psychiatry | Madison, Wisconsin | Nov. 10–16 | Dr. Hans H. Reese | University of Wisconsin, and Wisconsin State General Hospital | — |

It will be noted that, in a number of these proposed courses, the definite date or dates and maximum and minimum registration have not yet been determined. The fees for all courses will be $20 per week to members of the College; $40 per week for non-members; no charge to medical officers on active duty.

A detailed bulletin of the spring courses is in press and will promptly be mailed, together with a registration form, to every member of the College and to non-members who have requested this information.

The postgraduate bulletin of autumn courses will be published in the early summer.

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### Course in Internal Medicine

A general course in the principles and practice of Internal Medicine will be given at the Massachusetts General Hospital in Boston, Massachusetts from April 1 to 19, inclusive, under the Directorship of Dr. J. H. Means, F.A.C.P., who is Jackson Professor of Clinical Medicine at the Harvard Medical School and Chief of Medical Service of the Massachusetts General Hospital.

This proposed course will stress the fundamentals of Internal Medicine and will be limited to a maximum of eighty (80) registrants.

Various members of the Harvard Medical School faculty, who are serving in other Boston hospitals and institutions, will be invited to participate in the presentation of this course.

Registration will begin on or after January 1, 1946.

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### Courses in General Medicine

An intensive postgraduate course in *General and Internal Medicine* will be given in Philadelphia, Pa. at the Jefferson Hospital, from March 18 to 23, inclusive, under the Directorship of Dr. Hobart Reimann, F.A.C.P., who is Professor of Medicine of the Jefferson Medical College and Chief of the Medical Service of the Jefferson Hospital.

This course will deal with the recent advances in Internal Medicine and should be of particular value to returning veteran medical officers.

Registration will be limited to one hundred (100) applicants, and will begin on or after January 1, 1946.

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A course in *General Medicine*, under the Directorship of Dr. James E. Paullin, F.A.C.P., in coöperation with Dr. Eugene A. Stead, who is Professor of Medicine at Emory University, will be given in Atlanta, Georgia from April 22 to 27, inclusive.

The institutions and hospitals listed for the course are: Emory University Medical School in conjunction with the Piedmont, Grady, Emory University and Georgia Baptist Hospitals.

Registration will be limited to a maximum of twenty-five (25) men, and it is expected that a complete outline of the course will be available shortly after January 1, 1946.

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### Course in Cardiology

A course in Cardiology will be given in Philadelphia, Pa. by a composite faculty, under the Directorship of Dr. William G. Leaman, Jr., F.A.C.P., who is Professor of Medicine of the Woman's Medical College of Pennsylvania.

Sessions will be held during the daytime at the Philadelphia General Hospital. In the evening, an interesting and rather unusual program, devoted to the basic sciences and their relation to cardiology, will be given by the members of the preclinical faculty of the Woman's Medical College in Philadelphia. Recent advances in cardiac anatomy, physiology, pharmacology and pathology in their relation to cardiac

problems will be presented. This program promises information valuable to the general internist as well as to the cardiologist.

Registration will be limited to one hundred (100) applicants, beginning on or after January 1, 1946.

Incidentally, this course directly precedes the annual session of the College, to be held in Philadelphia from May 13 to 17, inclusive.

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### Information for the Veteran Medical Officer

During the past two months the office of the Educational Director of the College has been in touch with our Regents and Governors, as well as with the Deans and the Professors of Medicine at teaching centers throughout the country, requesting practical information concerning assistantships, residencies, teaching positions and research assignments available to veteran medical officers who are members of the College and who have recently been returned to inactive duty status or will shortly be released from military service.

Nearly all the larger hospitals and medical schools have expanded their residency and teaching facilities to accommodate their own returning veterans insofar as possible. The demand for specialty training far exceeds the supply of immediately available facilities. As a result, many institutions already have a waiting list of their own graduates and a large backlog of applications from non-graduates who are desirous of further training in the field of Internal Medicine.

As the plan of demobilization of medical officers progresses, the present situation will become more acute, and those who are considering further graduate training in hospital residencies should take definite steps immediately to secure their desired appointments in advance.

It is believed that the best procedure will be for the veteran to contact the medical school from which he graduated and the hospital or other institution where he had served his internship and/or residency prior to his entrance into the armed forces. A well qualified internist should be able to establish himself in a large city in the practice of Internal Medicine without encountering too many obstacles. Smaller towns offer many opportunities of moderate promise, while in the rural areas there is a dearth of well trained clinicians.

Many State and County Medical Societies are performing yeoman work in organizing local placement aid for their former members about to return from active military duty. The American Medical Association has compiled a general overall view of the situation throughout the country. More specific information can be obtained by writing directly to the Bureau of Information of the American Medical Association, or the State and County Medical Societies concerned in the matter.

The Educational Director will be glad to discuss, in a general way, the problems of an individual veteran member either by correspondence or, preferably, by an interview at College Headquarters.

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Brigadier General Hugh J. Morgan, F.A.C.P., Director of Medical Consultants Division, and Colonel Francis R. Dieuaide, F.A.C.P., Chief of Tropical Disease Treatment Branch, have made an inspection of medical services in the Pacific, Japan and Japanese territory, and have been surveying problems concerned with internal medicine, according to the Office of the Surgeon General of the Army.

During a two-week stop-over in Manila, a special study was made of the comparison between patients from Asia suffering starvation, and Europe's starvation cases. Health studies were recently made in Europe by Brigadier General James S. Simmons, F.A.C.P., Chief of Preventive Medicine Service, and Colonel Thomas B. Turner, Director of Civil Public Health and Nutrition.

## *OBITUARIES*

### DR. HAROLD DEAN PALMER

Dr. Harold Dean Palmer, F.A.C.P., Philadelphia, Pa.; born, Fairmont, Minnesota, June 12, 1901; attended Culver Military Academy and Hamline University of St. Paul; B.S., 1924, University of Minnesota; M.D., 1927, University of Minnesota Medical School; intern, 1927–29, Philadelphia General Hospital, Philadelphia; Resident Psychiatrist, 1929–31, Pennsylvania Hospital, Philadelphia; Professor of Psychiatry, Woman's Medical College of Pennsylvania; Associate in Psychiatry, University of Pennsylvania School of Medicine; also on the faculty of the University of Pennsylvania Graduate School of Medicine; Senior Psychiatrist, Institute of the Pennsylvania Hospital; Psychiatrist and Consultant in Department for Nervous and Mental Diseases, Pennsylvania Hospital; Visiting Physician and Psychiatrist, Philadelphia General Hospital; Psychiatrist, Health Service, University of Pennsylvania; member, Philadelphia County Medical Society, American Neurological Association, American Psychiatric Association, Philadelphia Neurological Society, Philadelphia Psychiatric Society, American Association for the Advancement of Science, and Research Council on Alcoholism; Fellow, American Medical Association, College of Physicians of Philadelphia, and American College of Physicians (the latter since 1941); Diplomate, American Board of Psychiatry and Neurology; author of numerous published papers, and contributor to Hughes Practice of Medicine and Oxford Medicine.

Thus is recorded in bare outline the career of a distinguished psychiatrist who died much too soon in Philadelphia on November 20, 1945. His loss will be keenly felt by American medicine. His professional attainments were of the very highest order. He was a careful student and scientific worker and he provided an influence which is very much needed in current psychiatry. His point of view tended to be sanely organic. He exerted a very healthy leavening influence which frequently modified too restricted psychogenic viewpoints and often his careful and verified data were an antidote against overly speculative, armchair thinking.

He was a gentleman in the real sense of the word and in his everyday life, he exhibited true nobility of character. Psychiatry has lost a skilled and constructive advocate and those of us who knew Harold Palmer intimately have lost a dear friend.

EDWARD A. STRECKER, M.D., F.A.C.P.

### DR. ABRAHAM TRASOFF

Dr. Abraham Trasoff, Philadelphia, Pennsylvania, who died suddenly on November 24, 1945 had long been active in the medical affairs of the city.

He received his degree of Doctor of Medicine from the Medico-Chirurgical Medical College in 1915. For the following year he interned at Mount

Sinai Hospital where he had since been closely affiliated. During his association at Mount Sinai Hospital, Dr. Trasoff served as Chief of the Out-Patient Medical Department, Adjunct Visiting Physician, Chief of the Department of Allergy and Attending Visiting Physician.

In addition to his work for the Mount Sinai Hospital, Dr. Trasoff at one time was Clinical Assistant at Jefferson Medical College of Philadelphia and the Jewish Hospital. He was also Consultant in Diseases of the Chest for the United States Veterans Bureau.

Dr. Trasoff closely identified himself with organized medical associations, both local and national. He was a member of many societies and he had been a Fellow of The American College of Physicians since 1940. He had also contributed extensively to the medical literature.

It is with sincere regret that the passing of Dr. Abraham Trasoff is acknowledged.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

## DR. JULES M. BRADY

Dr. Jules Brady died at his home in St. Louis on September 6, 1945, at the age of 68, after an extremely busy life in the field of pediatrics. Having served, after graduating from medical school, in St. Louis municipal hospitals from 1898 to 1902, he became associated with St. Louis University first in the Department of Pathology; later with the Department of Pediatrics. He was Associate Professor of Pediatrics from 1918 to 1940, when he became Emeritus.

He devoted the greater part of his professional life to the care of infants and small children at St. Ann's Foundling Asylum, and his name is linked in local medical circles with that institution. He was a careful and exacting teacher, and a conscientious physician.

He was a member of the American Academy of Pediatrics, and Diplomate, The American Board of Pediatrics. He was a Fellow of the American College of Physicians since 1920.

RALPH KINSELLA, M.D., F.A.C.P.,
Governor for Missouri

## DR. ALPHEUS FELCH JENNINGS

Dr. Jennings was born in Detroit, Michigan, on June 22, 1884. He died of uremia on November 16, 1945.

Dr. Jennings was graduated (A.B.) from the University of Michigan in 1907, and from Harvard Medical School in 1910, following which he served as medical house physician at the Massachusetts General Hospital. At the end of this service he entered private practice in Detroit. For many years he served on the staff of Harper Hospital in Detroit, and since 1936 was Chief of Staff and President of the Board of Trustees of the Charles

Godwin Jennings Hospital. Dr. Jennings' medical interests were wide. He was extramural lecturer in internal medicine at the University of Michigan; Assistant Professor of Clinical Medicine at Wayne University; Consultant in Medicine, U. S. Marine Hospital; former 1st Vice President and Editor of the Transactions, American Therapeutic Society. In addition to these activities he was a Diplomate of the American Board of Internal Medicine, a member of the American Clinical and Climatological Society, and had served as Chairman of the Medical Section of the Michigan State Medical Society, and Vice Chairman of the Medical Section of the American Medical Association. In 1922 Dr. Jennings became a Fellow, American College of Physicians, and, following the death of his father, the late Charles Godwin Jennings, he acted as General Chairman of the 20th Annual Session of the College at Detroit in 1936.

In World War I Dr. Jennings served as Assistant Chief of the Medical Service at Camp Custer and later in France, being discharged with the rank of Major.

The loss of his scientific and clinical abilities will be felt by all who knew and were devoted to him—his patients, students and his associates.

Dr. Jennings is survived by his widow, and three sons: Charles Godwin Jennings II, Capt. M.C., A.U.S., Frederick Anderson Jennings and Richard Hall Jennings, Lt., U. S. Naval Reserve.

Douglas Donald, M.D., F.A.C.P.,
Governor for Michigan

## DR. FERDINAND MICHAEL JORDAN

Ferdinand Michael Jordan, M.D., F.A.C.P., White Plains, New York, died August 14, 1945, at the age of forty-three, of uremia and polycystic kidneys. Dr. Jordan was born at Scranton, Pennsylvania, January 22, 1902; M.D., 1925, University of Pennsylvania School of Medicine; intern, 1925–26, Misericordia Hospital, Philadelphia; postgraduate work at the Mayo Clinic, 1926–1931; M.S. in Medicine, 1929, Mayo Foundation of the University of Minnesota; for many years attending physician, Grasslands Hospital, Valhalla; member of the Associate Staff, St. Agnes and White Plains Hospitals; Diplomate, American Board of Internal Medicine, with special certification in gastro-enterology; member, Kings County Medical Society, New York State Medical Society, and Fellow, American Medical Association.

Dr. Jordan has been a Fellow of the American College of Physicians since 1936. His passing is recorded with deep regret.

Asa L. Lincoln, M.D., F.A.C.P.,
Governor for Eastern New York